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COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A POTASSIUM ION CHANNEL MODULATOR FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DAMAGE

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority from the following Provisional Applications: Serial No. 60/465,268 filed on April 24, 2003, Serial No. 60/464,830 filed on April 23, 2003, and Serial No. 60/464,499 filed on April 22, 2003, all of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention provides compositions and methods for the treatment of central nervous system damage. More particularly, the invention is directed toward a combination therapy for the treatment or prevention of ischemic-mediated central nervous system damage including ischemic stroke, or central nervous system damage resulting from traumatic injury, comprising the administration to a subject of a potassium ion channel modulator in combination with a cyclooxygenase-2 selective inhibitor.

BACKGROUND OF THE INVENTION

[0003] The continued increase in the incidence of ischemic-mediated central nervous system damage, including ischemic stroke, provides compelling evidence that there is a continuing need for better treatment strategies. Stroke, for example, is consistently the second or the third leading cause of death annually and the leading producer of disability among adults in the United States and western countries. Moreover, roughly 10% of patients with stroke become heavily handicapped, often needing attendant care.

[0004] Within the 1990's decade, the pathology underlying ischemic-mediated central nervous system injury was elucidated. Generally speaking, the normal amount of perfusion to brain gray matter is 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs only when the flow of blood falls below a certain level (approximately 8-10 mL/100 g of brain tissue/min) while at slightly higher levels the tissue remains alive but not able to function. For example, most strokes culminate in a core area of cell death

(infarction) in which blood flow is so drastically reduced that the cells usually cannot recover. This threshold seems to occur when cerebral blood flow is 20 percent of normal or less. Without neuroprotective agents, nerve cells facing 80 to 100 percent ischemia will be irreversibly damaged within a few minutes. Surrounding the ischemic core is another area of tissue called the "ischemic penumbra" or "transitional zone" in which cerebral blood flow is between 20 and 50 percent of normal. Cells in this area are endangered, but not yet irreversibly damaged. Thus in the acute stroke, the affected central core brain tissue may die while the more peripheral tissues remain alive for many years after the initial insult, depending on the amount of blood the brain tissue receives.

[0005] At the cellular level, if left untreated, rapidly within the core infarction, and over time within the ischemic penumbra, brain or spinal cell injury and death progress in stepwise manner. Without adequate blood supply, brain or spinal cells lose their ability to produce energy, particularly adenosine triphosphate (ATP). When this energy failure occurs, brain or spinal cells become damaged and will die if critical thresholds are reached. Immediate cell death within the ischemic core is typically necrotic, while cell death in the penumbra may be either necrotic or apoptotic. It is believed that there are an immense number of mechanisms at work causing brain or spinal cell damage and death following energy failure. Each of these mechanisms represents a potential route for intervention. One of the ways brain cells respond to energy failure is by elevating the concentration of intracellular calcium. Worsening this and driving the concentrations to dangerous levels is the process of excitotoxicity, in which brain cells release excessive amounts of glutamate, a neurotransmitter. This stimulates chemical and electrical activities in receptors on other brain cells, which leads to the degradation and destruction of vital cellular structures. Brain cells ultimately die as a result of the actions of calcium-activated proteases (enzymes which digest cell proteins), lipases (enzymes which digest cell membranes) and free radicals formed as a result of the ischemic cascade.

[0006] Interventions have been directed toward salvaging the ischemic penumbra and reducing its size. Restoration of blood flow is the first step toward rescuing the tissue within the penumbra. Therefore, timely recanalization of an occluded vessel to restore perfusion in both the penumbra and in the ischemic

core is one treatment option employed. Partial recanalization also markedly reduces the size of the penumbra as well. Moreover, intravenous tissue plasminogen activator and other thrombolytic agents have been shown to have clinical benefit if they are administered within a few hours of symptom onset. Beyond this narrow time window, however, the likelihood of beneficial effects is reduced and hemorrhagic complications related to thrombolytic agents become excessive, seriously compromising their therapeutic value. Hypothermia decreases the size of the ischemic insult in both anecdotal clinical and laboratory reports. In addition, a wide variety of agents have been shown to reduce infarct volume in animal models. These agents include pharmacologic interventions that involve thrombolysis, calcium channel blockade, and cell membrane receptor antagonism. Successful treatment of stroke victims remains a high-unmet medical need. To date, no effective neuroprotective therapy exists to treat stroke. There is a continuing need for improved treatment regimes following ischemic-mediated central nervous system injury.

[0007] Neuroprotective agents have been shown to extend the time during which neurons within the ischemic penumbra remain viable (Albers, (1997) Am. J. Cardiol. 804(4C):4d-10d). Toward that end, several studies indicate that treatment with a potassium ion channel modulator following ischemic-mediated central nervous system injury may be beneficial. Potassium ion channel modulators have been shown to exploit natural endogenous protective mechanisms that come into play during ischemia (Purcell H., et al., (1999) J. Clin. Cardiol. (2):12-14). Furthermore, it has been suggested that several potassium ion channel modulators have shown neuroprotective effect in animal models of ischemia. In one study, for example, it was demonstrated that potassium ion channel modulator administration to rats showed significant neuroprotective effect against focal cerebral ischemia (Sargent CA, et al., (1991) J. Pharmacol. Exp. Ther. (259)(1):97-103). Another study demonstrated a significant improvement in reperfusion function to ischemic rats administered a potassium ion channel modulator compared to control animals receiving saline (Grover GJ, et al., (1989) J. Pharmacol. Exp. Ther. (251)(1):98-104). A study in patients with spinal cord injury demonstrated the restoration of action potential conduction in damaged, poorly myelinated nerve fibers, and the enhancement of synaptic transmission

following administration of a potassium channel modulator (Stein, J., http://www.pslgroup.com/dg/22068A.htm).

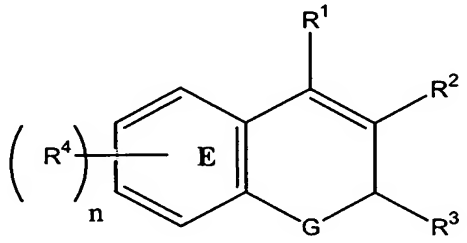
[0008] Several studies indicate that cyclooxygenase-2 is involved in the inflammatory component of the ischemic cascade. Inflammation is thought to play a contributory role in stroke progression (Vila et al., Stroke 2000;31:2325-2329). Since stroke is associated with a heterogeneous cascade of molecular events, experts presently believe that stroke will not be effectively treated with one "magic bullet" but that a combination of drugs that treat different components of the molecular cascade will be the most effective treatment strategy...i.e. that of polypharmacy.

[0009] Cyclooxygenase-2 expression is known to be induced in the central nervous system following ischemic injury. In one study, it was shown that treatment with a cyclooxygenase-2 selective inhibitor reduced infarct volume in mice subjected to ischemic brain injury (Nagayama et al., (1999) J. Cereb. Blood Flow Metab.19(11):1213-19). A similar study showed that cyclooxygenase-2 deficient mice have a significant reduction in brain injury produced by occlusion of the middle cerebral artery when compared to mice that express cyclooxygenase-2 (Iadecola et al., (2001) PNAS 98:1294-1299). Another study demonstrated that treatment with cyclooxygenase-2 selective inhibitor results in improved behavioral deficits induced by reversible spinal ischemia in rabbits (Lapchak et al., (2001) Stroke 32(5):1220-1230).

SUMMARY OF THE INVENTION

[0010] Among the several aspects of the invention is provided a method and a composition for the treatment of reduced blood flow to the central nervous system in a subject. The composition comprises a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, and the method comprises administering to the subject a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof in combination with a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

[0011] In one embodiment, the cyclooxygenase-2 selective inhibitor is a member of the chromene class of compounds. For example, the chromene compound may be a compound of the formula:



(I)

[0012] wherein:

[0013] n is an integer which is 0, 1, 2, 3 or 4;

[0014] G is O, S or NR^a;

[0015] R^a is alkyl;

[0016] R^1 is selected from the group consisting of H and aryl;

[0017] R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

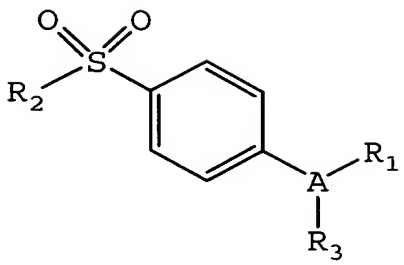
[0018] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

[0019] each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

[0020] or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical;

[0021] or prodrug thereof.

[0022] In another embodiment, the cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof comprises a compound of the formula:



[0023] wherein

[0024] A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

[0025] R_1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R_1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0026] R_2 is selected from the group consisting of methyl or amino; and

[0027] R_3 is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl.

[0028] In one embodiment, the potassium ion channel modulator is a potassium ion channel blocker. In one alternative of this embodiment, the

potassium ion channel blocker is a voltage-gated potassium channel blocker. In another alternative of this embodiment, the potassium ion channel blocker is a calcium-activated potassium channel blocker. In a further alternative of this embodiment, the potassium ion channel blocker is an ATP-sensitive potassium channel blocker. In a still further alternative of this embodiment, the potassium ion channel blocker is a two-pore potassium channel blocker.

[0029] In another embodiment, the potassium ion channel modulator is a potassium ion channel opener. In one alternative of this embodiment, the potassium ion channel opener is a voltage-gated potassium channel opener. In another alternative of this embodiment, the potassium ion channel opener is a calcium-activated potassium channel opener. In a further alternative of this embodiment, the potassium ion channel opener is an ATP-sensitive potassium channel opener. In a still further alternative of this embodiment, the potassium ion channel opener is a two-pore potassium channel opener.

[0030] Other aspects of the invention are described in more detail below.

ABBREVIATIONS AND DEFINITIONS

[0031] The term "acyl" is a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and trifluoroacetyl.

[0032] The term "alkenyl" is a linear or branched radical having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl.

[0033] The terms "alkenyl" and "lower alkenyl" also are radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "cycloalkyl" is a saturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to

about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0034] The terms "alkoxy" and "alkyloxy" are linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

[0035] The term "alkoxyalkyl" is an alkyl radical having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

[0036] The term "alkoxycarbonyl" is a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl porions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

[0037] Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" is a linear, cyclic or branched radical having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

[0038] The term "alkylamino" is an amino group that has been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino,

N,N-dimethylamino, N,N-diethylamino or the like.

[0039] The term "alkylaminoalkyl" is a radical having one or more alkyl radicals attached to an aminoalkyl radical.

[0040] The term "alkylaminocarbonyl" is an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above.

[0041] The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

[0042] The term "alkylthio" is a radical containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

[0043] The term "alkylthioalkyl" is a radical containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

[0044] The term "alkylsulfinyl" is a radical containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

[0045] The term "alkynyl" is a linear or branched radical having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about

six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[0046] The term "aminoalkyl" is an alkyl radical substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like.

[0047] The term "aminocarbonyl" is an amide group of the formula -C(=O)NH2.

[0048] The term "aralkoxy" is an aralkyl radical attached through an oxygen atom to other radicals.

[0049] The term "aralkoxyalkyl" is an aralkoxy radical attached through an oxygen atom to an alkyl radical.

[0050] The term "aralkyl" is an aryl-substituted alkyl radical such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

[0051] The term "aralkylamino" is an aralkyl radical attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" are amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

[0052] The term "aralkylthio" is an aralkyl radical attached to a sulfur atom.

[0053] The term "aralkylthioalkyl" is an aralkylthio radical attached through a sulfur atom to an alkyl radical.

[0054] The term "aroyl" is an aryl radical with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

[0055] The term "aryl", alone or in combination, is a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with

one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

[0056] The term "arylamino" is an amino group, which has been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

[0057] The term "aryloxyalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent oxygen atom.

[0058] The term "arylthioalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

[0059] The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", is -(C=O)-.

[0060] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", is -CO2H.

[0061] The term "carboxyalkyl" is an alkyl radical substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which are lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl.

[0062] The term "cycloalkenyl" is a partially unsaturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl.

[0063] The term “cyclooxygenase-2 selective inhibitor” is a compound able to inhibit cyclooxygenase-2 without significant inhibition of cyclooxygenase-1. Typically, it includes compounds that have a cyclooxygenase-2 IC_{50} of less than about 0.2 micro molar, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more typically, of at least 100. Even more typically, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 micro molar, and more preferably of greater than 10 micro molar. Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic

acid used in the present method may inhibit enzyme activity through a variety of mechanisms. By the way of example, and without limitation, the inhibitors used in the methods described herein may block the enzyme activity directly by acting as a substrate for the enzyme.

[0064] The term "halo" is a halogen such as fluorine, chlorine, bromine or iodine.

[0065] The term "haloalkyl" is a radical wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically included are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" is a radical having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

[0066] The term "heteroaryl" is an unsaturated heterocyclyl radical. Examples of unsaturated heterocyclyl radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen

atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also includes radicals where heterocyclyl radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

[0067] The term "heterocyclyl" is a saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radical, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

[0068] The term "heterocyclylalkyl" is a saturated and partially unsaturated heterocyclyl-substituted alkyl radical, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

[0069] The term "hydrido" is a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH2-) radical.

[0070] The term "hydroxyalkyl" is a linear or branched alkyl radical having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower

hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

[0071] The term "modulate," as used herein, refers to a change in the biological activity of a biologically active molecule. Modulation can be an increase or a decrease in activity, a change in binding characteristics, or any other change in the biological, functional, or immunological properties of biologically active molecules.

[0072] The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product; that is the "pharmaceutically acceptable" material is relatively safe and/or non-toxic, though not necessarily providing a separable therapeutic benefit by itself. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiologically acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzy1ethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[0073] The term "prodrug" refers to a chemical compound that can be converted into a therapeutic compound by metabolic or simple chemical processes within the body of the subject. For example, a class of prodrugs of COX-2 inhibitors is described in US Patent No. 5,932,598, herein incorporated by reference.

[0074] The term "subject" for purposes of treatment includes any human or animal subject who has reduced blood flow to the central nervous system. The

subject can be a domestic livestock species, a laboratory animal species, a zoo animal or a companion animal. In one embodiment, the subject is a mammal. In another embodiment, the mammal is a human being.

[0075] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, is a divalent radical $-SO_2-$. "Alkylsulfonyl" is an alkyl radical attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" are NH_2O_2S-.

[0076] The phrase "therapeutically-effective" is intended to qualify the amount of each agent (i.e. the amount of cyclooxygenase-2 selective inhibitor and the amount of potassium ion channel modulator) which will achieve the goal of improvement in disorder severity and the frequency of incidence over no treatment or treatment of each agent by itself.

[0077] The term "thrombotic event" or "thromboembolic event" includes, but is not limited to arterial thrombosis, including stent and graft thrombosis, cardiac thrombosis, coronary thrombosis, heart valve thrombosis, pulmonary thrombosis and venous thrombosis. Cardiac thrombosis is thrombosis in the heart. Pulmonary thrombosis is thrombosis in the lung. Arterial thrombosis is thrombosis in an artery such as a carotid artery thrombosis. Coronary thrombosis is the development of an obstructive thrombus in a coronary artery, often causing sudden death or a myocardial infarction. Venous thrombosis is thrombosis in a vein. Heart valve thrombosis is a thrombosis on a heart valve. Stent thrombosis is thrombosis resulting from and/or located in the vicinity of a vascular stent. Graft thrombosis is thrombosis resulting from and/or located in the vicinity of an implanted graft, particularly a vascular graft.

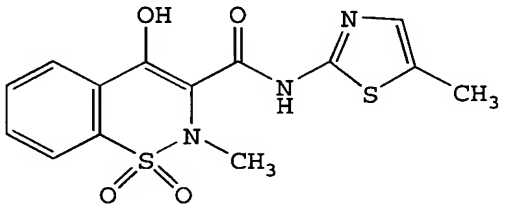
[0078] The term "vaso-occlusive event" includes a partial occlusion (including a narrowing) or complete occlusion of a blood vessel, a stent or a vascular graft. A vaso-occlusive event, as used herein, expressly excludes an occlusion or event resulting from heart disease, as the term is defined herein.

Description of the Preferred Embodiments

[0079] The present invention provides a combination therapy comprising the administration to a subject of a therapeutically effective amount of a COX-2 selective inhibitor in combination with a therapeutically effective amount of a potassium ion channel modulator. The combination therapy is used to treat or prevent damage to a central nervous system cell resulting from a reduction in blood flow or traumatic injury. When administered as part of a combination therapy, the COX-2 selective inhibitor together with the potassium ion channel modulator provide enhanced treatment options as compared to administration of either the potassium ion channel modulator or the COX-2 selective inhibitor alone.

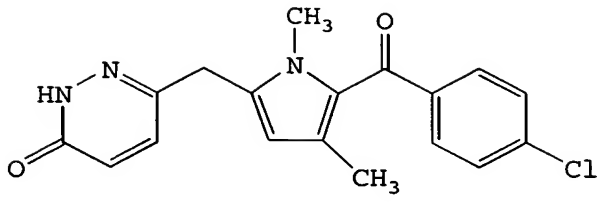
CYCLOOXYGENASE-2 SELECTIVE INHIBITORS

[0080] A number of suitable cyclooxygenase-2 selective inhibitors or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, may be employed in the composition of the current invention. In one embodiment, the cyclooxygenase-2 selective inhibitor can be, for example, the cyclooxygenase-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-1.



B-1

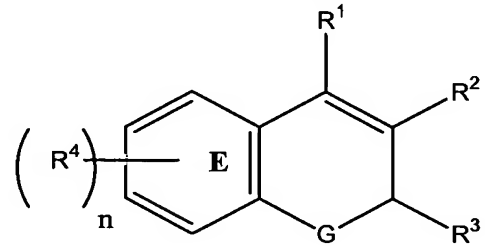
[0081] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is the cyclooxygenase-2 selective inhibitor, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-2.

1. 

B-2

[0082] In still another embodiment the cyclooxygenase-2 selective inhibitor is a chromene compound that is a substituted benzopyran or a substituted benzopyran analog, and even more typically, selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, dihydronaphthalenes or a compound having Formula *I* shown below and possessing, by way of example and not limitation, the structures disclosed in Table 1x. Furthermore, benzopyran cyclooxygenase-2 selective inhibitors useful in the practice of the present methods are described in U.S. Patent No. 6,034,256 and 6,077,850 herein incorporated by reference in their entirety.

[0083] In another embodiment, the cyclooxygenase-2 selective inhibitor is a chromene compound represented by Formula *I* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:

1. 

(I)

[0084] wherein:

[0085] n is an integer which is 0, 1, 2, 3 or 4;

[0086] G is O, S or NR^a;

[0087] R^a is alkyl;

[0088] R^1 is selected from the group consisting of H and aryl;

[0089] R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0090] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

[0091] each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

[0092] or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0093] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

[0094] n is an integer which is 0, 1, 2, 3 or 4;

[0095] G is O, S or NR^a;

[0096] R^1 is H;

[0097] R^a is alkyl;

[0098] R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0099] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0100] each R^4 is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

[0101] In a further embodiment, the cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)*, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

[0102] n is an integer which is 0, 1, 2, 3 or 4;

[0103] G is oxygen or sulfur;

[0104] R^1 is H;

[0105] R^2 is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

[0106] R^3 is lower haloalkyl, lower cycloalkyl or phenyl; and

[0107] each R^4 is H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or

[0108] R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0109] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0110] R^2 is carboxyl;

[0111] R^3 is lower haloalkyl; and

[0112] each R^4 is H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

[0113] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0114] n is an integer which is 0, 1, 2, 3 or 4;

[0115] R^3 is fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, or trifluoromethyl; and

[0116] each R^4 is H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0117] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0118] n is an integer which is 0, 1, 2, 3 or 4;

[0119] R^3 is trifluoromethyl or pentafluoroethyl; and

[0120] each R^4 is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0121] In yet another embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound having the structure of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0122] n = 4;

[0123] G is O or S;

[0124] R^1 is H;

[0125] R^2 is CO_2H;

[0126] R^3 is lower haloalkyl;

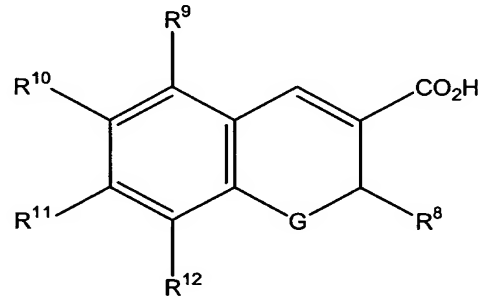
[0127] a first R^4 corresponding to R^9 is hydrido or halo;

[0128] a second R^4 corresponding to R^{10} is H, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, or 6- membered nitrogen-containing heterocyclosulfonyl;

[0129] a third R^4 corresponding to R^{11} is H, lower alkyl, halo, lower alkoxy, or aryl; and

[0130] a fourth R^4 corresponding to R^{12} is H, halo, lower alkyl, lower alkoxy, and aryl;

[0131] wherein Formula *(I)* is represented by Formula *(Ia)*:



(Ia)

a.

[0132] The cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound of having the structure of Formula *(Ia)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

[0133] R^8 is trifluoromethyl or pentafluoroethyl;

[0134] R^9 is H, chloro, or fluoro;

[0135] R^{10} is H, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, or morpholinosulfonyl;

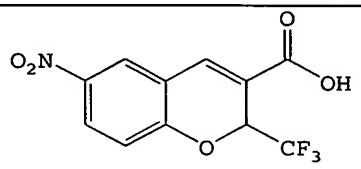
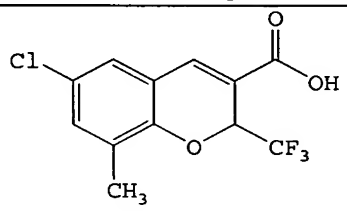
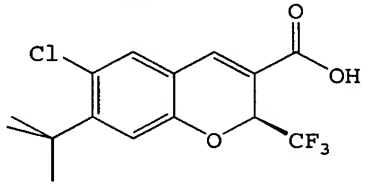
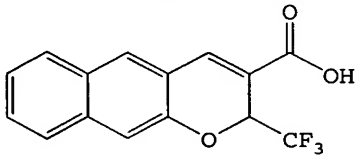
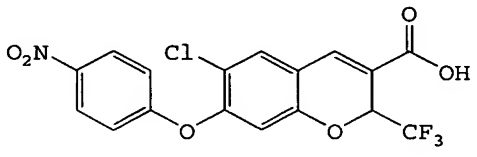
[0136] R^{11} is H, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, or phenyl; and

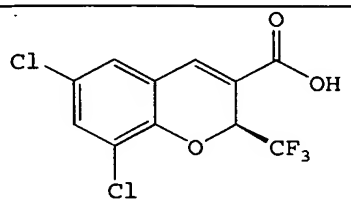
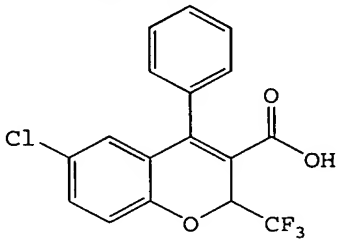
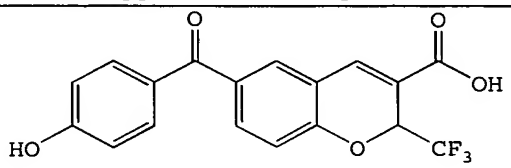
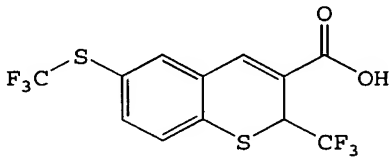
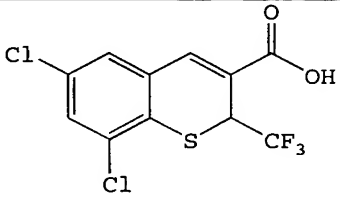
[0137] R^{12} is H, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, or phenyl.

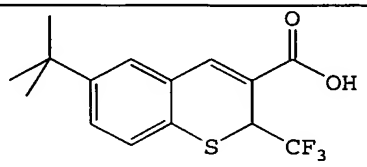
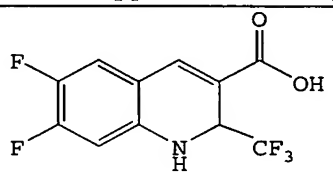
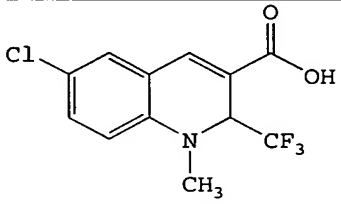
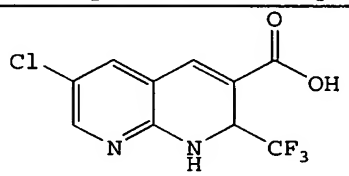
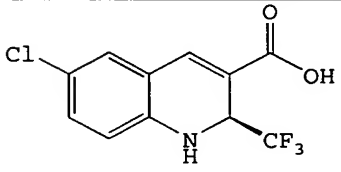
[0138] Examples of exemplary chromene cyclooxygenase-2 selective inhibitors are depicted in Table 1x below.

TABLE 1X

EXAMPLES OF CHROMENE CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

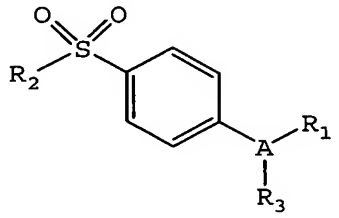
Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1- benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl) -2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

[0139] In a further embodiment, the cyclooxygenase-2 selective inhibitor is selected from the class of tricyclic cyclooxygenase-2 selective inhibitors

represented by the general structure of Formula *I*: or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:



II

[0140] A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

[0141] R_1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R_1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

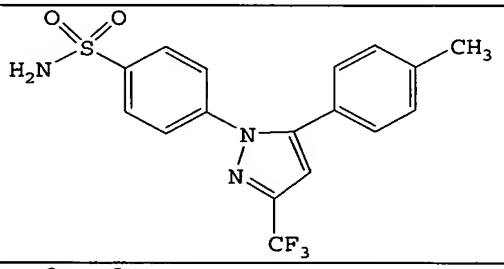
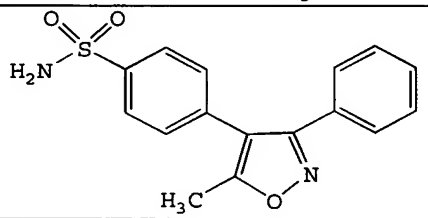
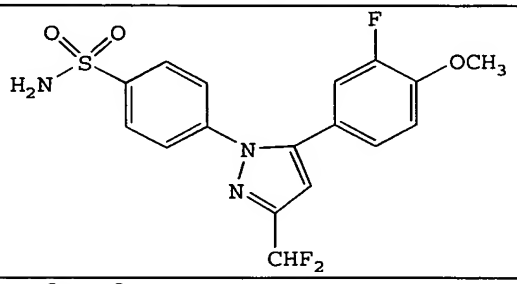
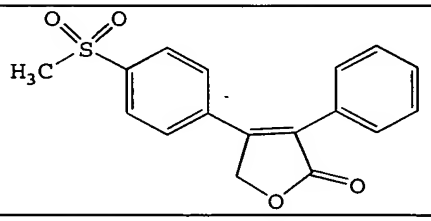
[0142] R_2 is selected from the group consisting of methyl or amino; and

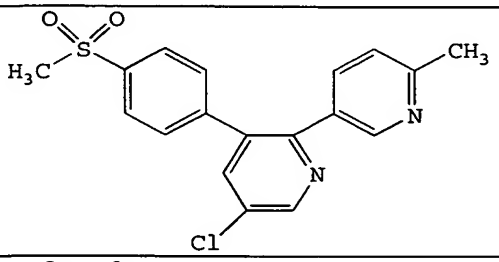
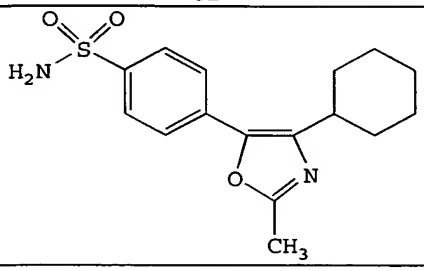
[0143] R_3 is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl.

[0144] In another embodiment, the cyclooxygenase-2 selective inhibitor represented by the above Formula *II* is selected from the group of compounds illustrated in Table 2x, consisting of celecoxib (B-18; U.S. Patent No. 5,466,823; CAS No. 169590-42-5), valdecoxib (B-19; U.S. Patent No. 5,633,272; CAS No. 181695-72-7), deracoxib (B-20; U.S. Patent No. 5,521,207; CAS No. 169590-41-4), rofecoxib (B-21; CAS No. 162011-90-7), etoricoxib (MK-663; B-22; PCT publication WO 98/03484), tilmacoxib (JTE-522; B-23; CAS No. 180200-68-4).

TABLE 2X

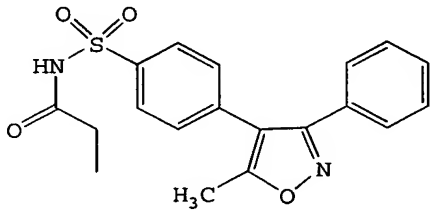
EXAMPLES OF TRICYCLIC CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

Compound Number	**Structural Formula**
B-18	
B-19	
B-20	
B-21	

Compound Number	Structural Formula
B-22	
B-23	

[0145] In still another embodiment, the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

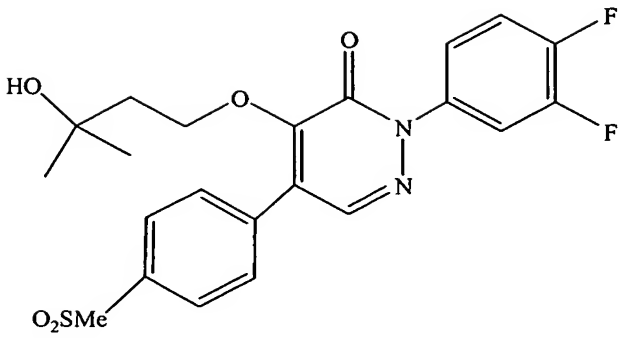
[0146] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is parecoxib (B-24, U.S. Patent No. 5,932,598, CAS No. 198470-84-7), which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, may be advantageously employed as a source of a cyclooxygenase inhibitor (US 5,932,598, herein incorporated by reference).



B-24

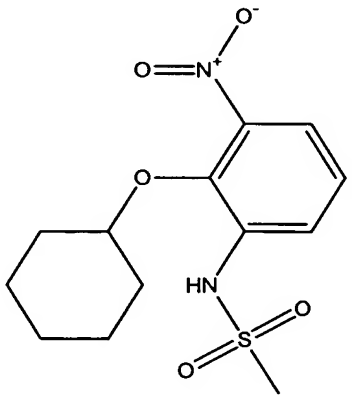
[0147] One form of parecoxib is sodium parecoxib.

[0148] In another embodiment of the invention, the compound having the formula B-25 or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-25 that has been previously described in International Publication number WO 00/24719 (which is herein incorporated by reference) is another tricyclic cyclooxygenase-2 selective inhibitor that may be advantageously employed.



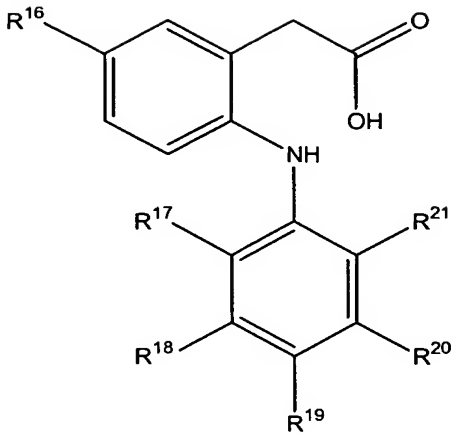
B-25

[0149] Another cyclooxygenase-2 selective inhibitor that is useful in connection with the method(s) of the present invention is N-(2-cyclohexyloxynitrophenyl)-methane sulfonamide (NS-398) having a structure shown below as B-26, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-26.



B-26

[0150] In yet a further embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(III)

[0151] wherein:

R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided that R^{17}, R^{18}, R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H.

[0152] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention is a compound that has the designation of COX 189 (lumiracoxib; B-211) and that has the structure shown in Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

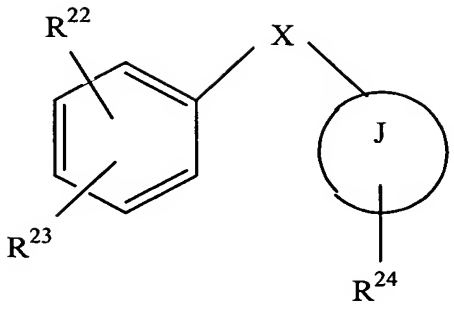
R^{16} is ethyl;

R^{17} and R^{19} are chloro;

R^{18} and R^{20} are hydrogen; and

and R^{21} is methyl.

[0153] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is represented by Formula *(IV)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(IV)

[0154] wherein:

X is O or S;

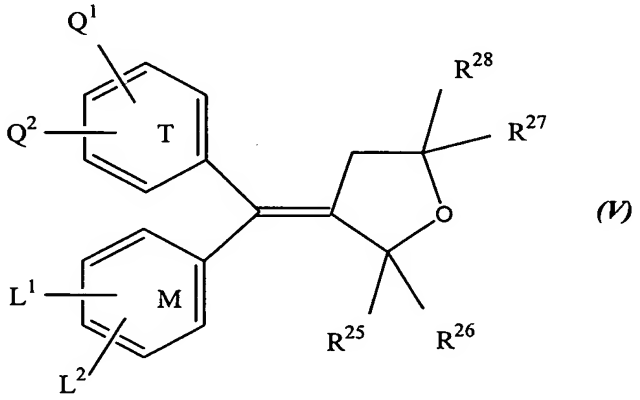
J is a carbocycle or a heterocycle;

R^{22} is $NHSO_2CH_3$ or F;

R^{23} is H, NO_2, or F; and

R^{24} is H, $NHSO_2CH_3$, or $(SO_2CH_3)C_6H_4$.

[0155] According to another embodiment, the cyclooxygenase-2 selective inhibitors used in the present method(s) have the structural Formula *(V)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(V)

[0156] wherein:

T and M independently are phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

Q^1, Q^2, L^1 or L^2 are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, or lower methoxy having from 1 to 6 carbon atoms; and

at least one of Q^1, Q^2, L^1 or L^2 is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or,

Q^1 and Q^2 are methylenedioxy; or

L^1 and L^2 are methylenedioxy; and

R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{25} and R^{26} are O; or,

R^{27} and R^{28} are O; or,

R^{25}, R^{26}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or,

R^{27}, R^{28}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms.

[0157] In another embodiment, the compounds N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the structure of Formula *(V)* are employed as cyclooxygenase-2 selective inhibitors.

[0158] In a further embodiment, compounds that are useful for the cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof used in connection with the method(s) of the present invention, the structures for which are set forth in Table 3x below, include, but are not limited to:

[0159] 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-27);

[0160] 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-28);

[0161] 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-29);

[0162] 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-30);

[0163] 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid (B-31);

[0164] 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-32);

[0165] 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-33);

[0166] 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-34);

[0167] 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-35);

[0168] 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-36);

[0169] 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-37);

[0170] 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-38);

[0171] 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-39);

[0172] 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-40);

[0173] 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-41);

[0174] 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-42);

[0175] 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-43);

[0176] 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-44);

[0177] 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-45);

[0178] 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-46);

[0179] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-47);

[0180] 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-48)

[0181] 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-49);

[0182] 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-50);

[0183] 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-51);

[0184] 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-52);

[0185] 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-53);

[0186] 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-54);

[0187] 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-55);

[0188] 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-56);

[0189] 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-57);

[0190] 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-58);

[0191] 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-59);

[0192] 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-60);

[0193] 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-61);

[0194] 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-62);

[0195] 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-63);

[0196] 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-64);

[0197] 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-65);

[0198] 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-66);

[0199] 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-67);

[0200] 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-68);

[0201] 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-69);

[0202] 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-70);

[0203] 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-71);

[0204] 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid (B-72);

[0205] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-73);

[0206] 3-[(3-Chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070 (B-74);

[0207] 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine (B-75);

[0208] 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone (B-76);

[0209] 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (B-77);

[0210] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole (B-78);

[0211] 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-79);

[0212] 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-80);

[0213] 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-81);

[0214] 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-82);

[0215] 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-83);

[0216] 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-84);

[0217] 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-85);

[0218] 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-86);

[0219] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-87);

[0220] 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-88);

[0221] 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-89);

[0222] 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-90);

[0223] 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-91);

[0224] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-92);

[0225] 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-93);

[0226] 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-94);

[0227] 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-95);

[0228] 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-96);

[0229] 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-97);

[0230] 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-98);

[0231] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-99);

[0232] 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-100);

[0233] 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-101);

[0234] 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-102);

[0235] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-103);

[0236] 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-104);

[0237] 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene (B-105);

[0238] 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-106);

[0239] 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-107);

[0240] 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-108);

[0241] 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-109);

[0242] 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-110);

[0243] 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (B-111);

[0244] 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (B-112);

[0245] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole (B-113);

[0246] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-114);

[0247] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole (B-115);

[0248] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole (B-116);

[0249] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole (B-117);

[0250] 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole (B-118);

[0251] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-119);

[0252] 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene (B-120);

[0253] 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide (B-121);

[0254] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene (B-122);

[0255] 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide (B-123);

[0256] 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-124);

[0257] 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-125);

[0258] 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile (B-126);

[0259] 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-127);

[0260] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-128);

[0261] 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-129);

[0262] 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-130);

[0263] 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-131);

[0264] 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-132);

[0265] 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-133);

[0266] 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-134);

[0267] 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-135);

[0268] 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-136);

[0269] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole (B-137);

[0270] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole (B-138);

[0271] 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (B-139);

[0272] 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole (B-140);

[0273] 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole (B-141);

[0274] 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-142);

[0275] 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-143);

[0276] 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-144);

[0277] 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-145);

[0278] 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-146);

[0279] 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-147);

[0280] 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole (B-148);

[0281] 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-149);

[0282] 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-150);

[0283] 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-151);

[0284] 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-152);

[0285] 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide (B-153);

[0286] N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide (B-154);

[0287] ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate (B-155);

[0288] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole (B-156);

[0289] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole (B-157);

[0290] 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-158);

[0291] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole (B-159);

[0292] 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole (B-160);

[0293] 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-161);

[0294] 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-162);

[0295] 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine (B-163);

[0296] 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-164);

[0297] 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (B-165);

[0298] 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (B-166);

[0299] 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole (B-167);

[0300] 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide (B-168);

[0301] 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-169);

[0302] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-170);

[0303] 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide (B-171);

[0304] 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-172);

[0305] 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-173);

[0306] 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-174);

[0307] 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-175);

[0308] 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-176);

[0309] 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-177);

[0310] 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-178);

[0311] 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide (B-179);

[0312] 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-180);

[0313] 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide (B-181);

[0314] 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-182);

[0315] 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-183);

[0316] 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-184);

[0317] 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-185);

[0318] 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide (B-186);

[0319] 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-187);

[0320] 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-188);

[0321] 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide (B-189);

[0322] ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate (B-190);

[0323] 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid (B-191);

[0324] 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole (B-192);

[0325] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (B-193);

[0326] 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole (B-194);

[0327] 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (B-195);

[0328] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-196);

[0329] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-197);

[0330] 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone (B-198);

[0331] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-199);

[0332] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-200);

[0333] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-201);

[0334] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-202);

[0335] 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-203);

[0336] 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-204);

[0337] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-205);

[0338] 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-206);

[0339] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-207);

[0340] [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide (B-208);

[0341] 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide (B-209);

[0342] 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (B-210);

[0343] [2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid or COX 189 (lumiracoxib; B-211);

[0344] N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide (B-212);

[0345] N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide or flosulide (B-213);

[0346] N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, soldium salt or L-745337 (B-214);

[0347] N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide or RWJ-63556 (B-215);

[0348] 3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one or L-784512 or L-784512 (B-216);

[0349] (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4(5H)-thiazolone or darbufelone (B-217);

[0350] CS-502 (B-218);

[0351] LAS-34475 (B-219);

[0352] LAS-34555 (B-220);

[0353] S-33516 (B-221);

[0354] SD-8381 (B-222);

[0355] L-783003 (B-223);

[0356] N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide or T-614 (B-224);

[0357] D-1367 (B-225);

[0358] L-748731 (B-226);

[0359] (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid or CT3 (B-227);

[0360] CGP-28238 (B-228);

[0361] 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389 (B-229);

[0362] GR-253035 (B-230);

[0363] 6-dioxo-9H-purin-8-yl-cinnamic acid (B-231);

[0364] S-2474 (B-232);

[0365] 4-[4-(methyl)-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

[0366] 4-(5-methyl-3-phenyl-4-isoxazolyl);

[0367] 2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine;

[0368] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl];

[0369] N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl];

[0370] 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

[0371] (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;

[0372] 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridzainone;

[0373] 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

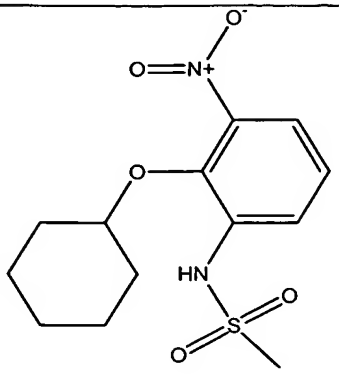
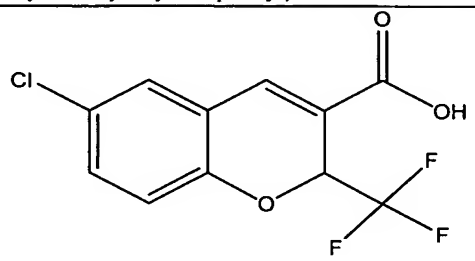
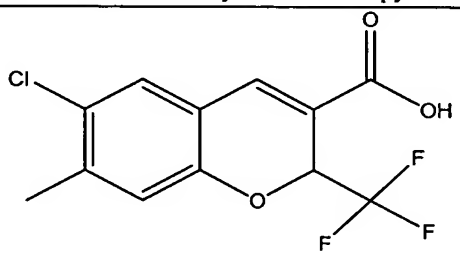
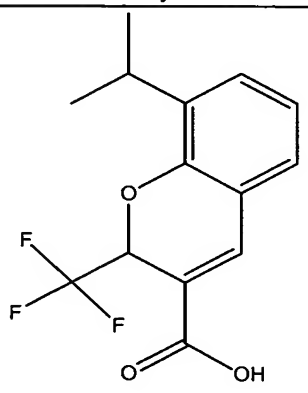
[0374] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

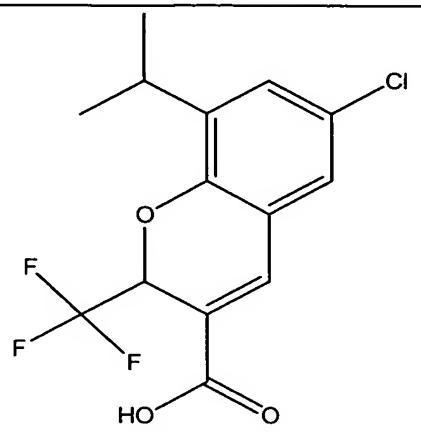
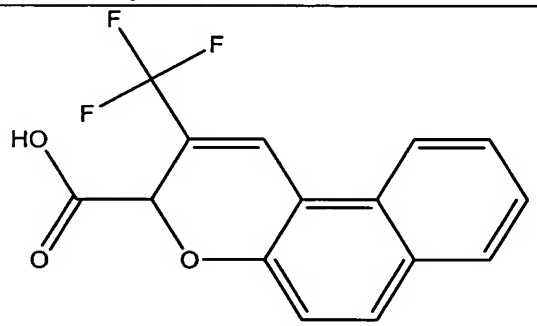
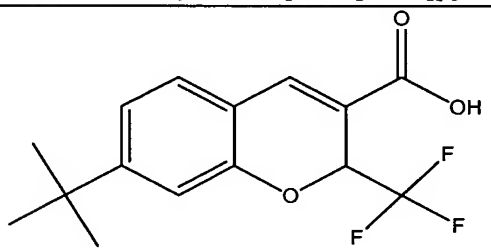
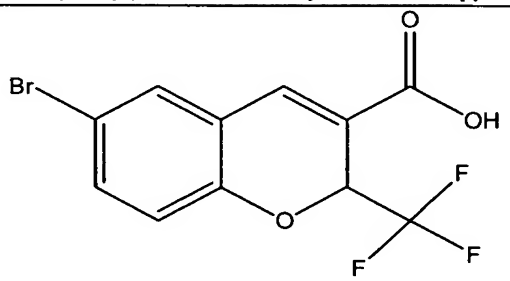
[0375] [2-(2,4-dichloro-6-ethyl-3,5-dimethyl-phenylamino)-5-propyl-phenyl]-acetic acid.

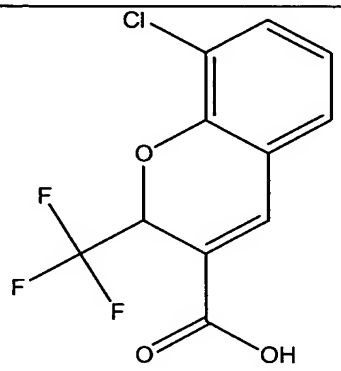
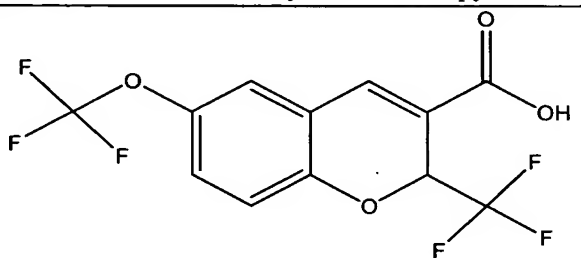
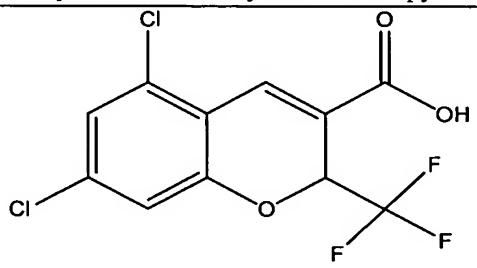
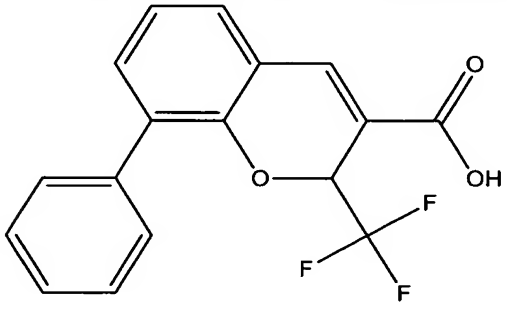
TABLE 3X

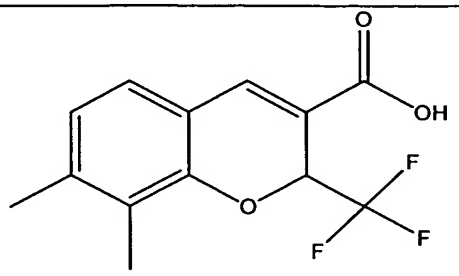
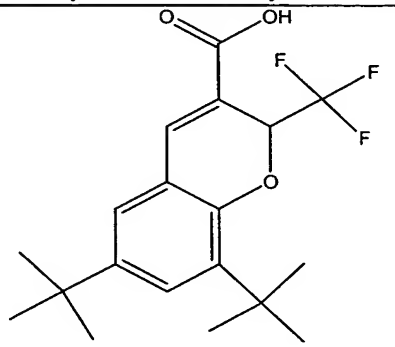
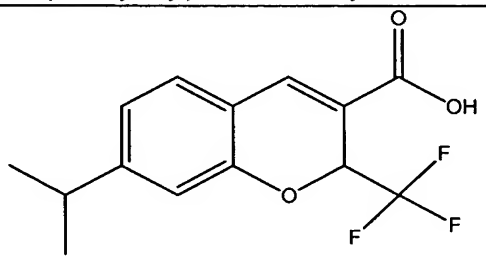
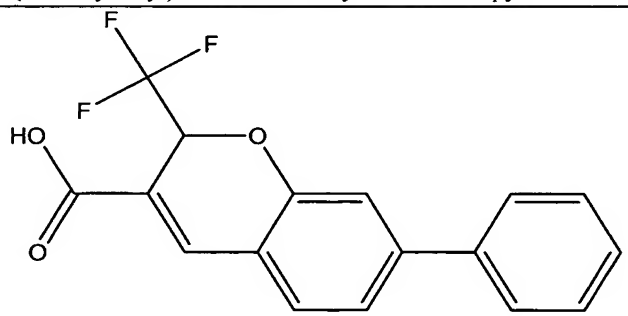
EXAMPLES OF CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

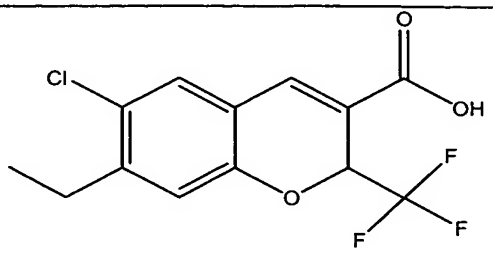
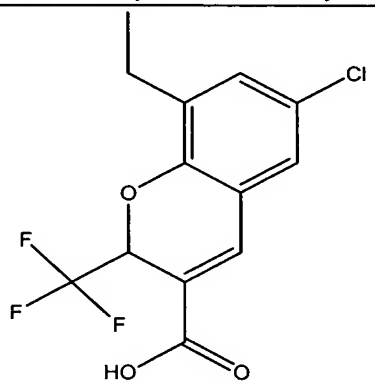
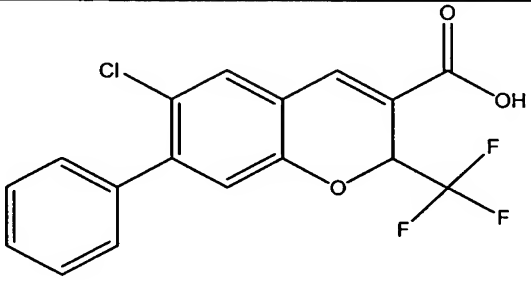
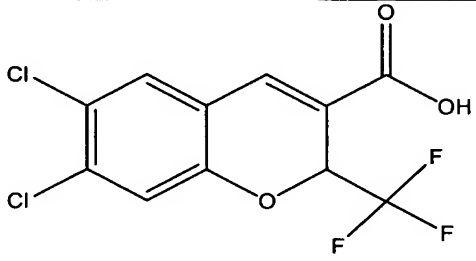
Compound Number	**Structural Formula**

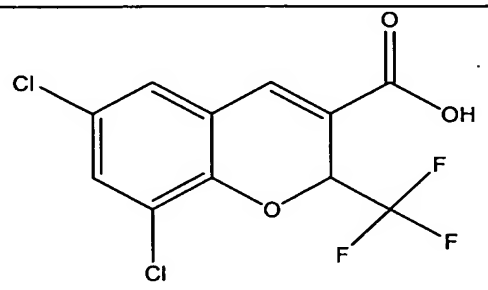
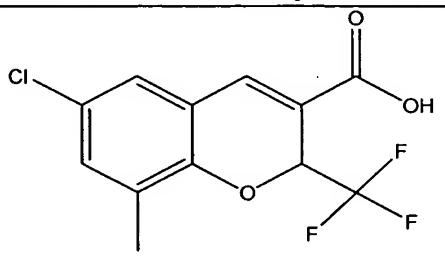
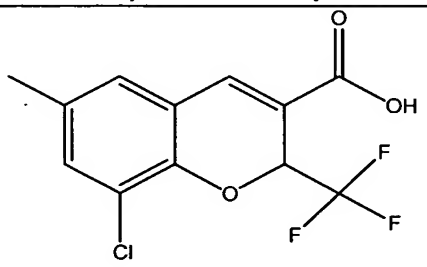
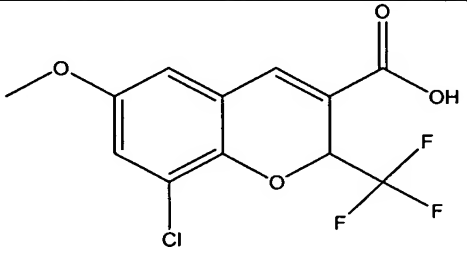
Compound Number	Structural Formula
B-26	 N-(2-cyclohexyloxynitrophenyl) methane sulfonamide or NS-398;
B-27	 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-28	 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-29	 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

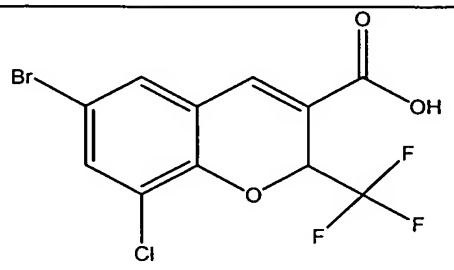
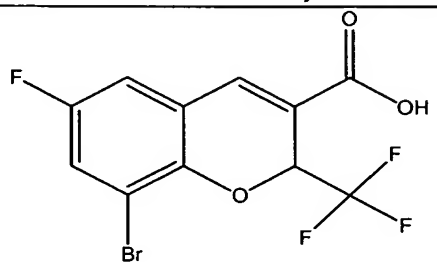
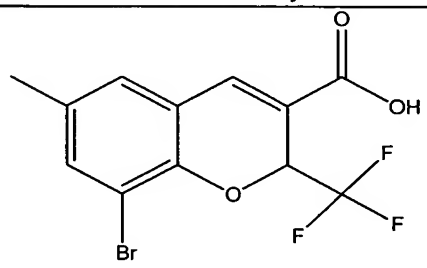
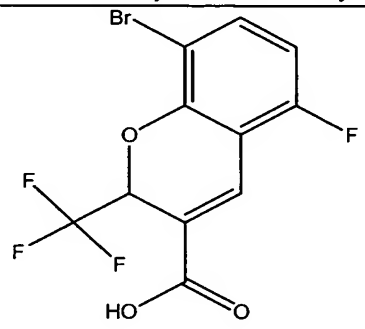
Compound Number	Structural Formula
B-30	 6-chloro-8-(1-methylethyl)-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-31	 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
B-32	 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-33	 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

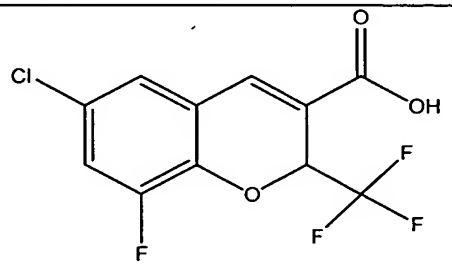
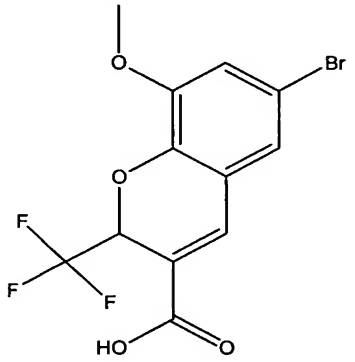
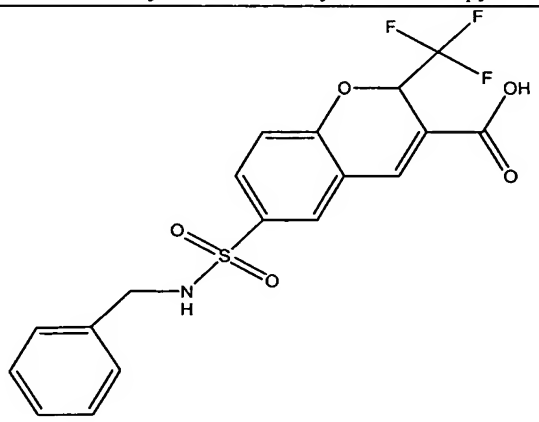
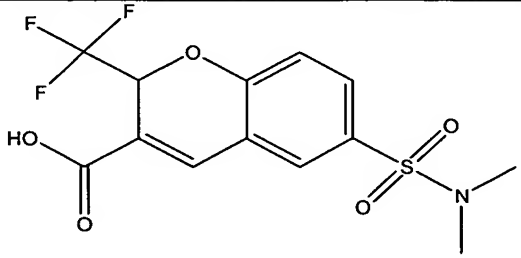
Compound Number	**Structural Formula**
B-34	 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-35	 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-36	 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-37	 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

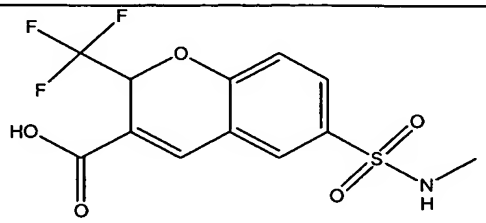
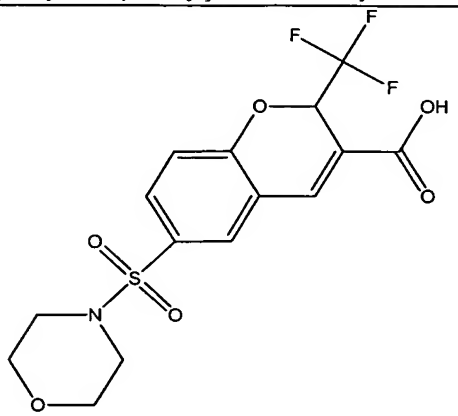
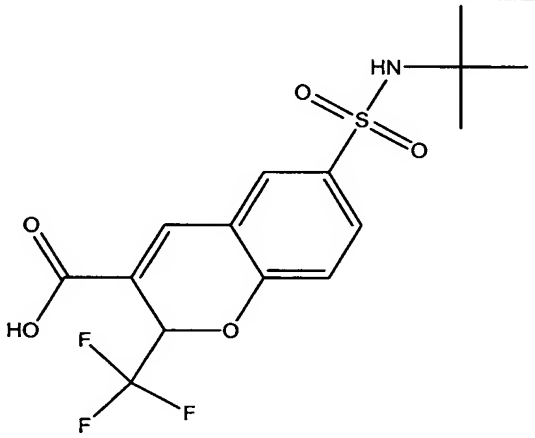
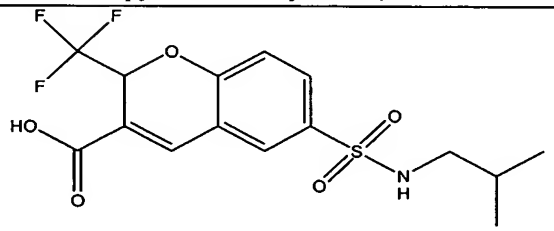
Compound Number	Structural Formula
B-38	 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-39	 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-40	 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-41	 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

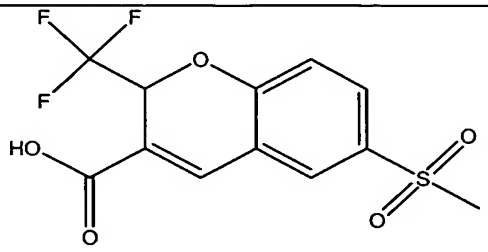
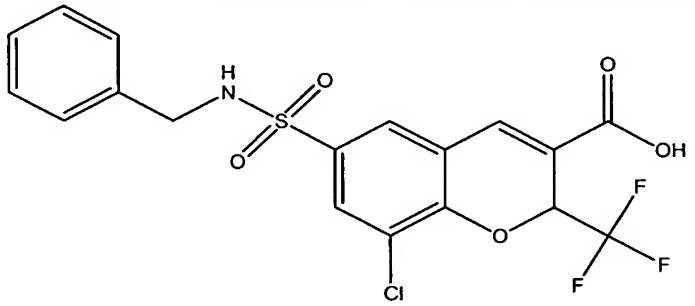
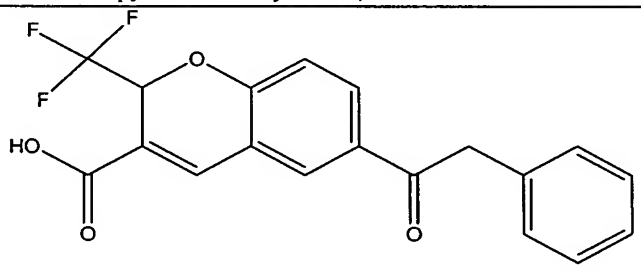
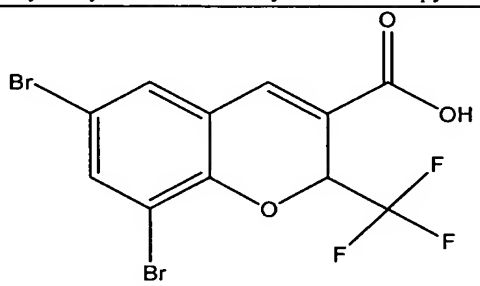
Compound Number	Structural Formula
B-42	 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-43	 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-44	 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-45	 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

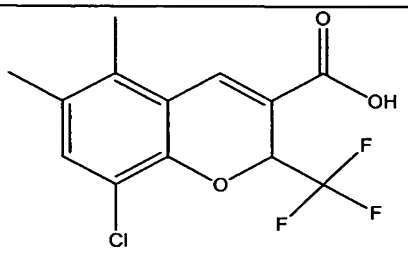
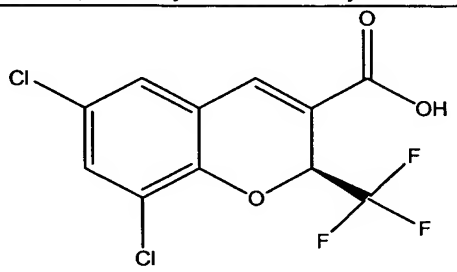
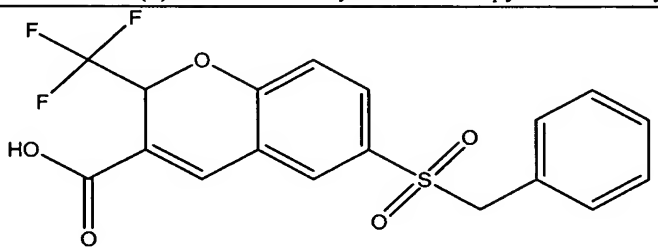
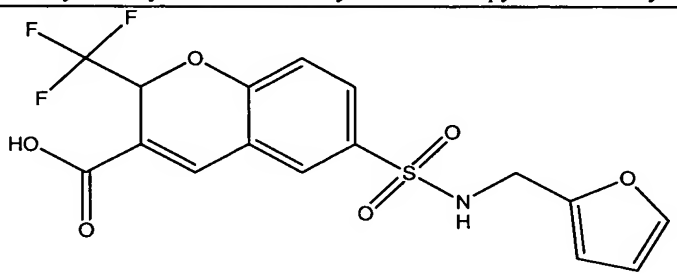
Compound Number	Structural Formula
B-46	 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-47	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-48	 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-49	 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

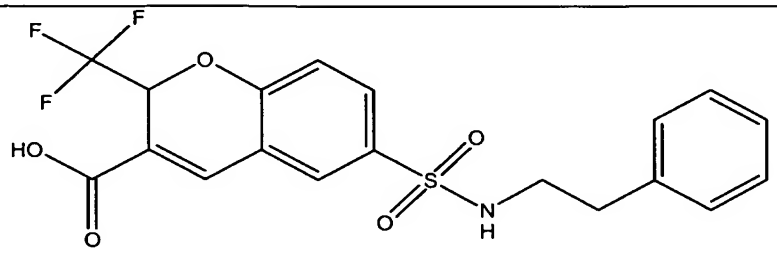
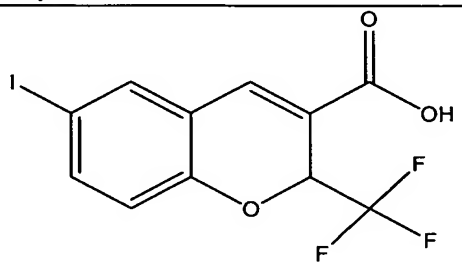
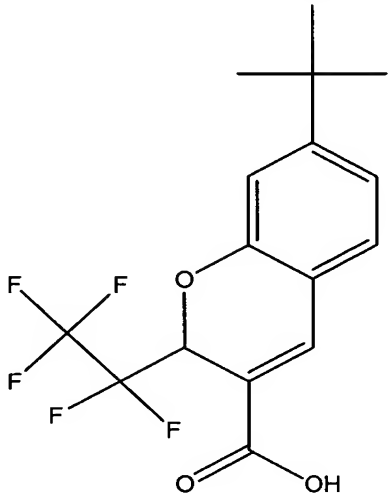
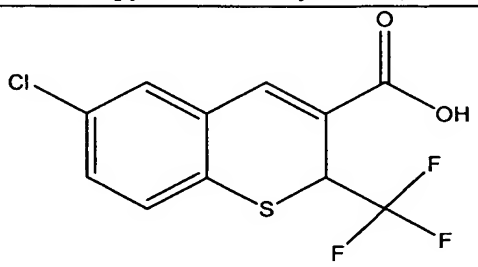
Compound Number	Structural Formula
B-50	 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-51	 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-52	 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-53	 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

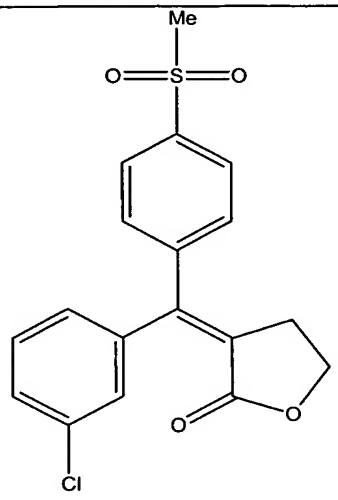
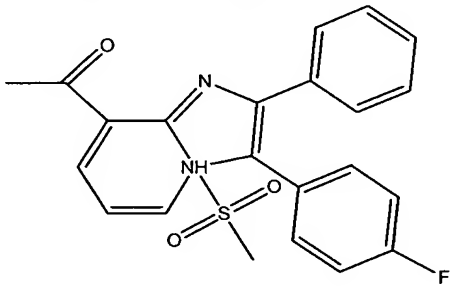
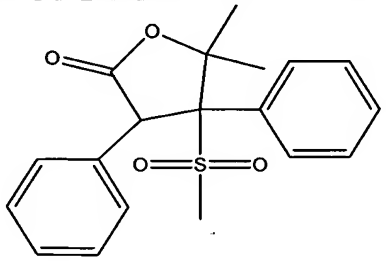
Compound Number	Structural Formula
B-54	 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-55	 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-56	 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-57	 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

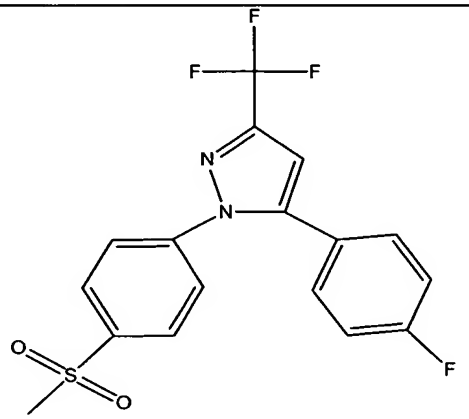
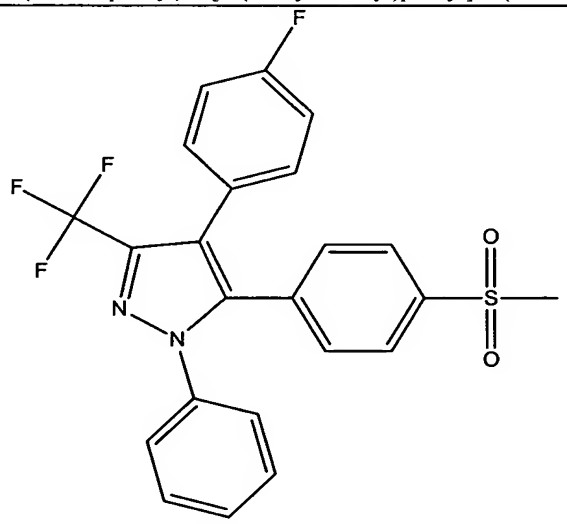
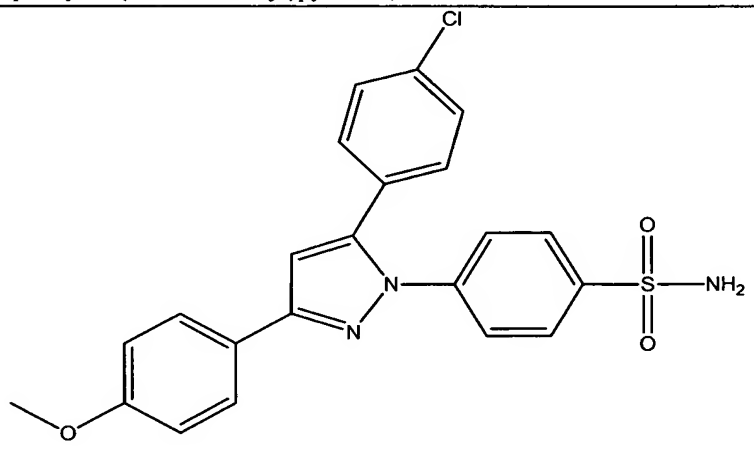
Compound Number	Structural Formula
B-58	 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-59	 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-60	 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-61	 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

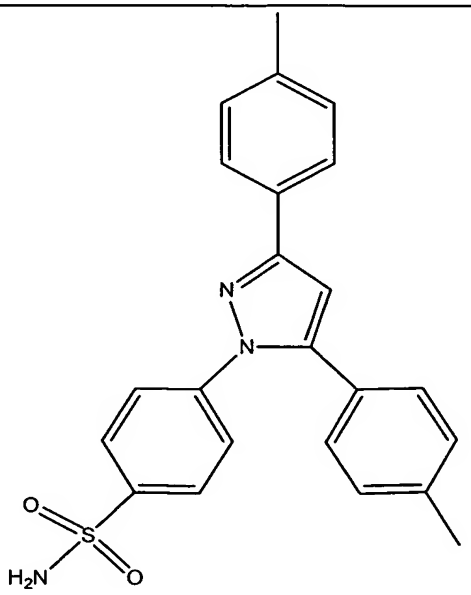
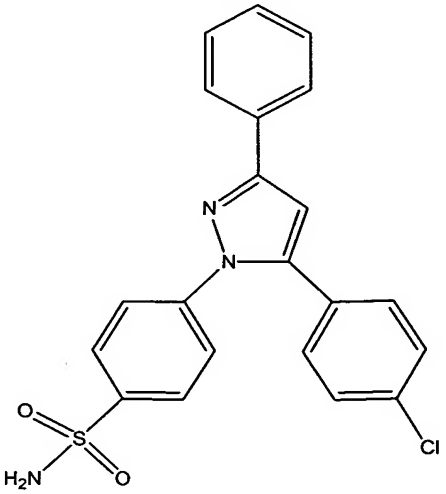
Compound Number	Structural Formula
B-62	 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-63	 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-64	 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-65	 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

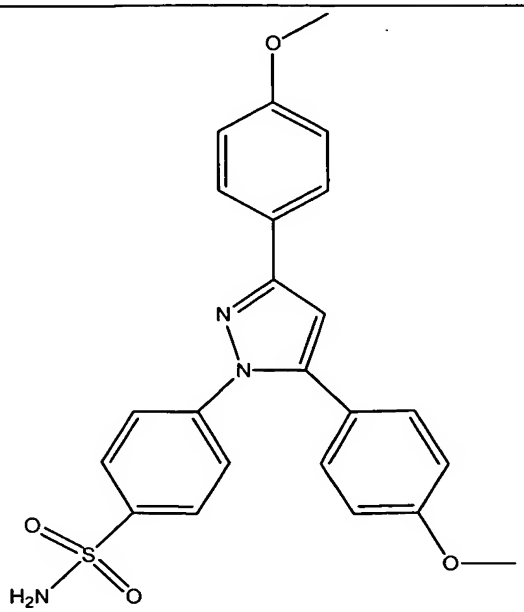
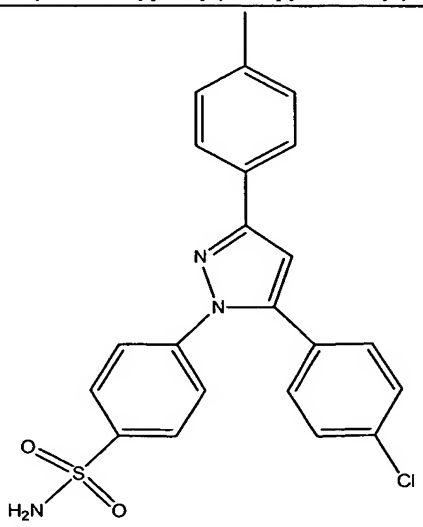
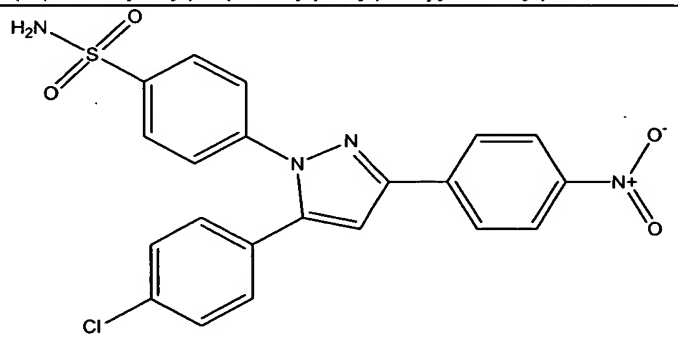
Compound Number	**Structural Formula**
B-66	 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-67	 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-68	 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-69	 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;

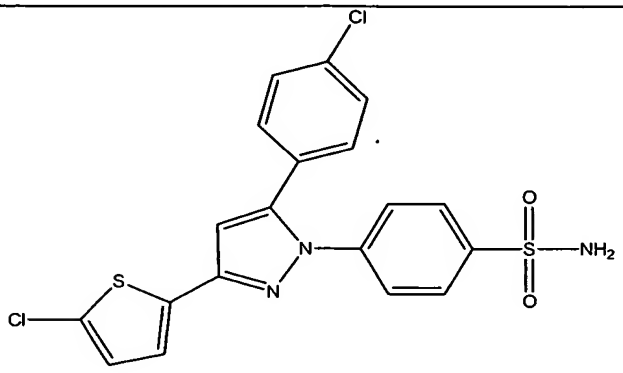
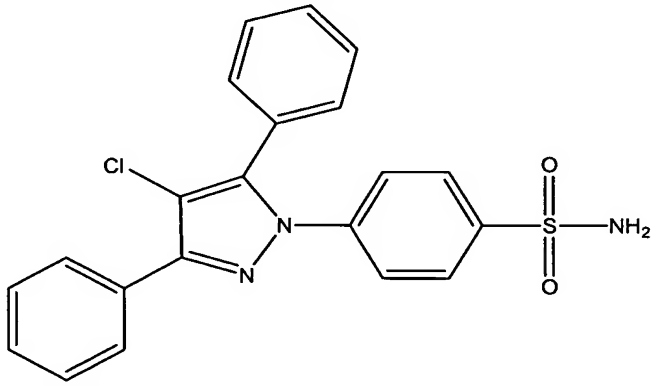
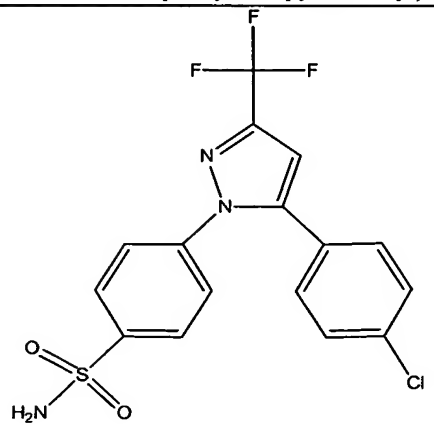
Compound Number	Structural Formula
B-70	 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran -3-carboxylic acid;
B-71	 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-72	 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H -1-benzopyran-3-carboxylic acid;
B-73	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

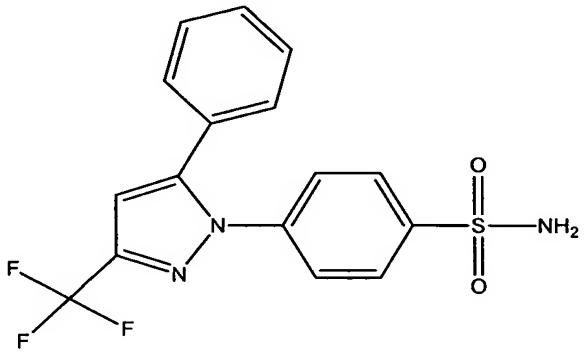
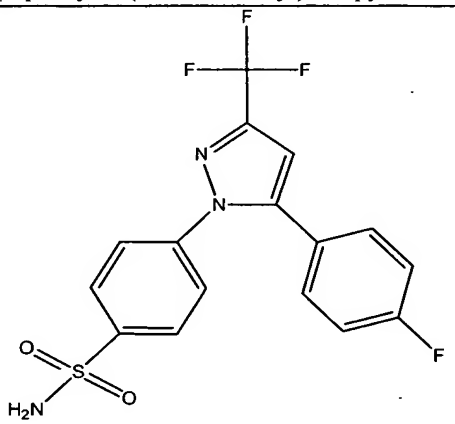
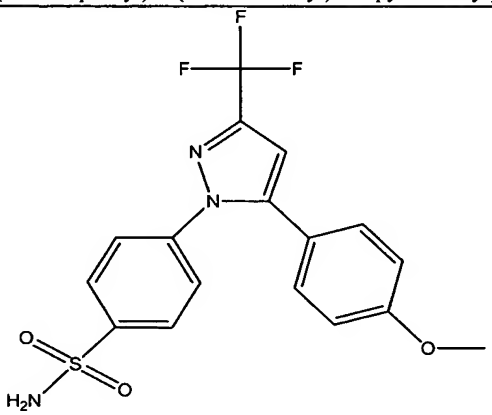
Compound Number	Structural Formula
B-74	 3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene] -dihydro-furan-2-one or BMS-347070;
B-75	 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;
B-76	 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

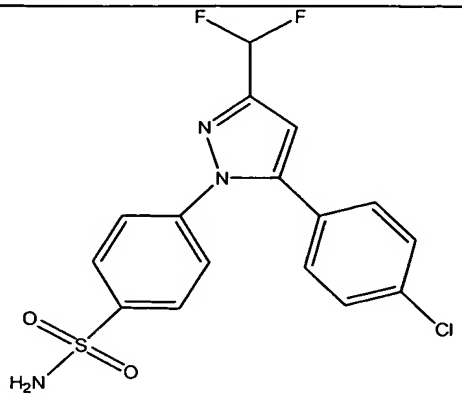
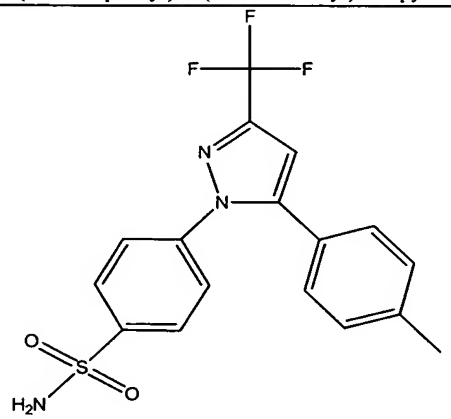
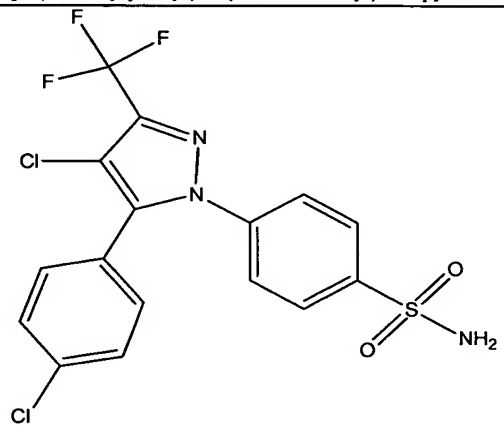
Compound Number	Structural Formula
B-77	 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;
B-78	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -1-phenyl-3-(trifluoromethyl)pyrazole;
B-79	 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide;

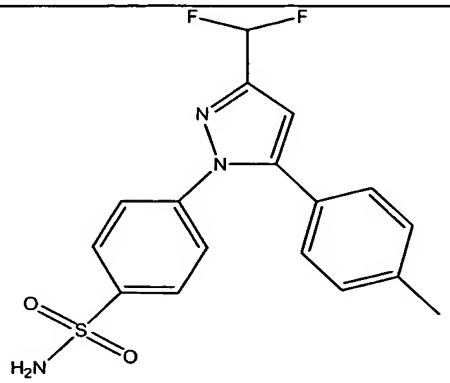
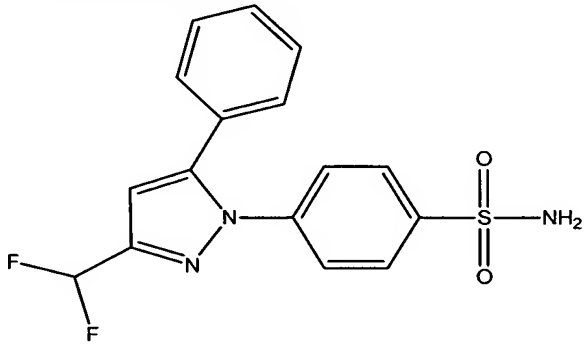
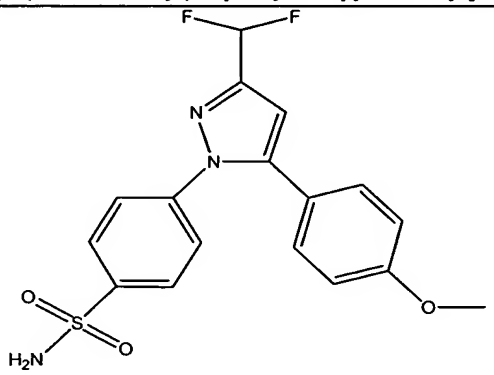
Compound Number	Structural Formula
B-80	 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-81	 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

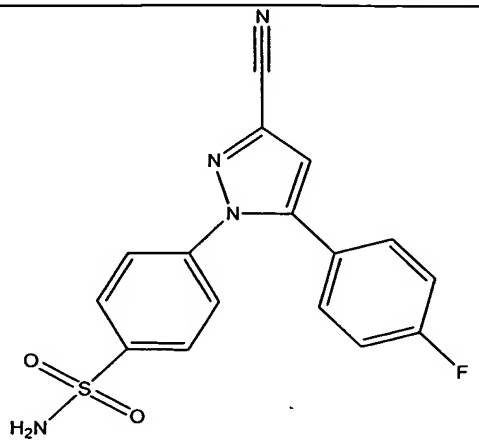
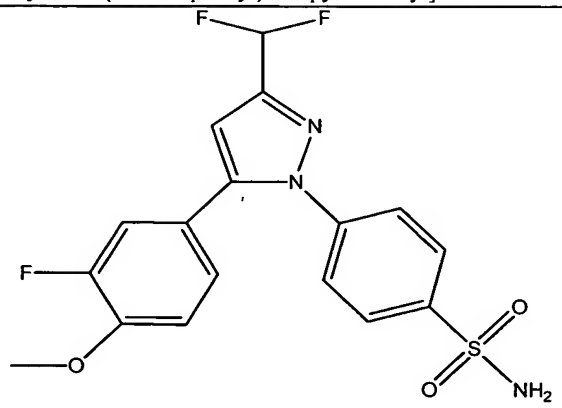
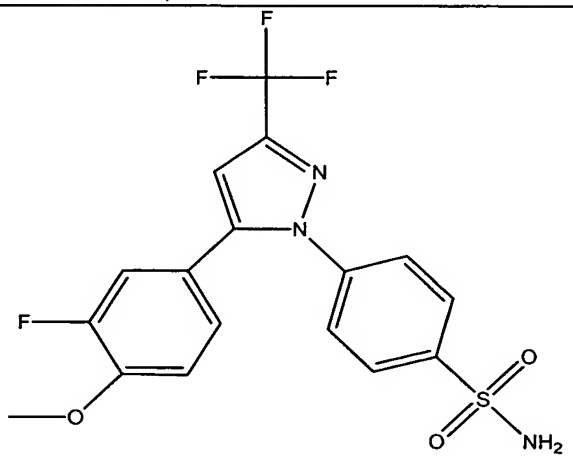
Compound Number	Structural Formula
B-82	 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-83	 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-84	 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

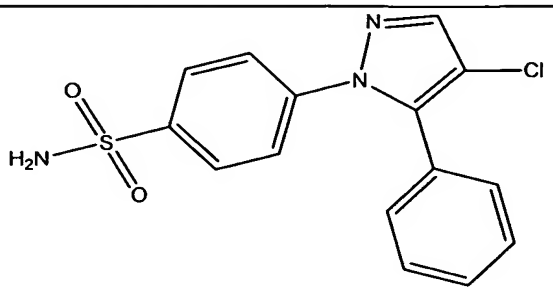
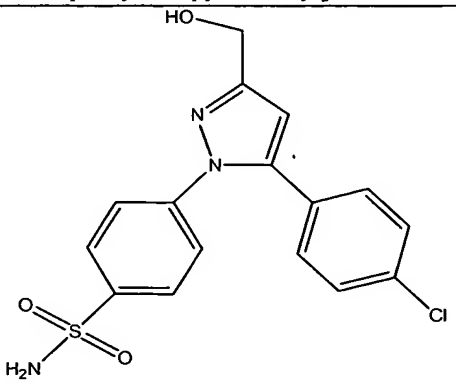
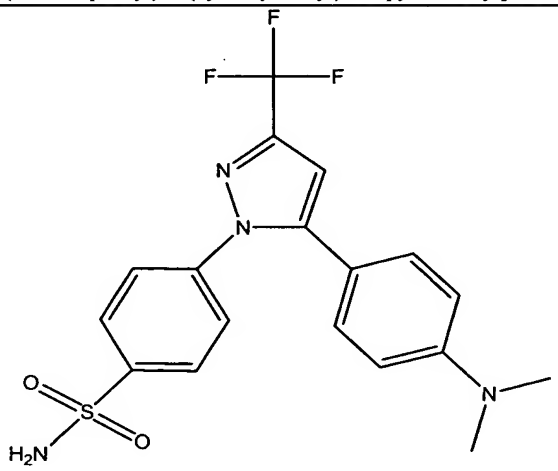
Compound Number	Structural Formula
B-85	 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-86	 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;
B-87	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

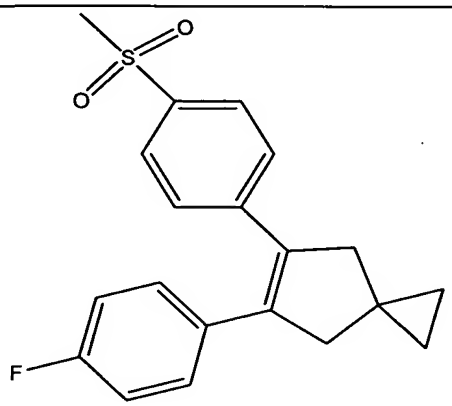
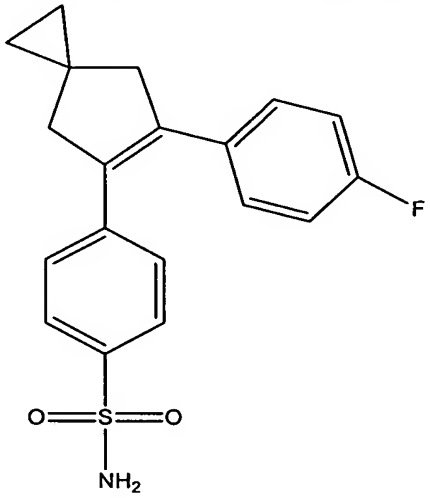
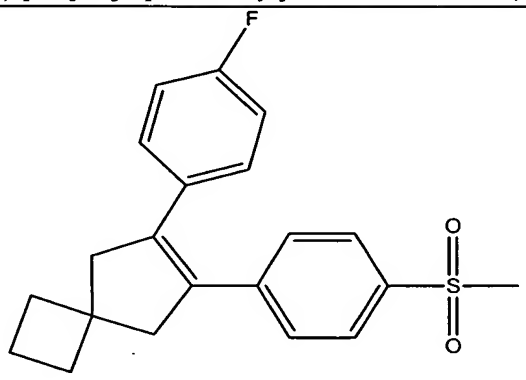
Compound Number	Structural Formula
B-88	 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-89	 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-90	 4[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

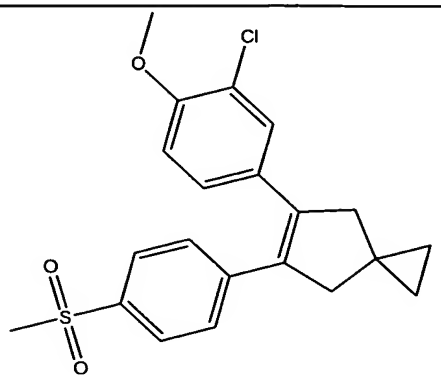
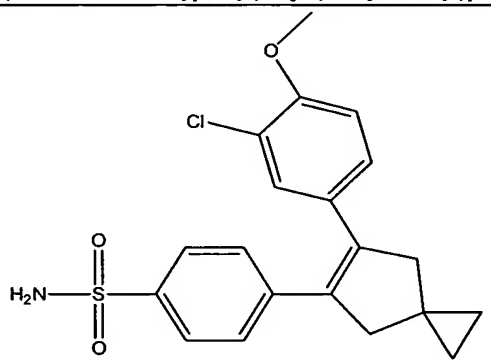
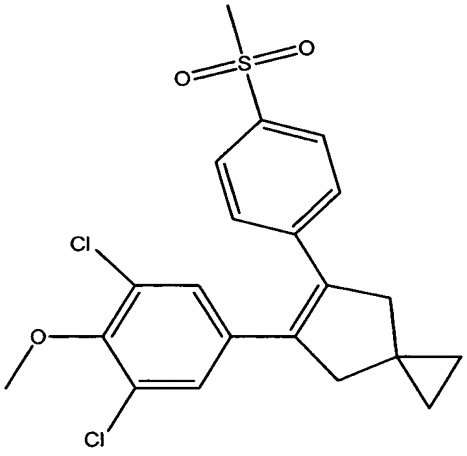
Compound Number	Structural Formula
B-91	 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-92	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-93	 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

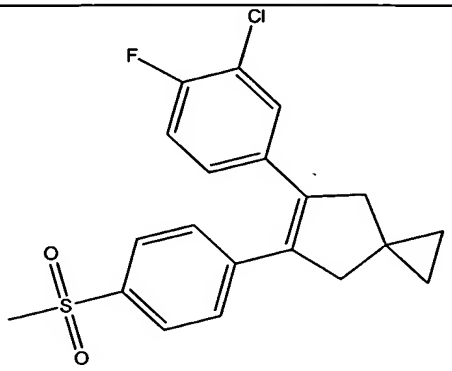
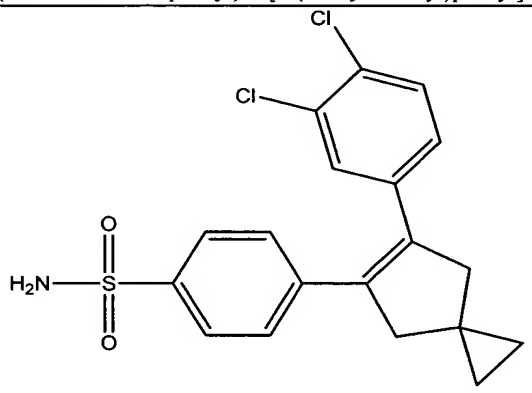
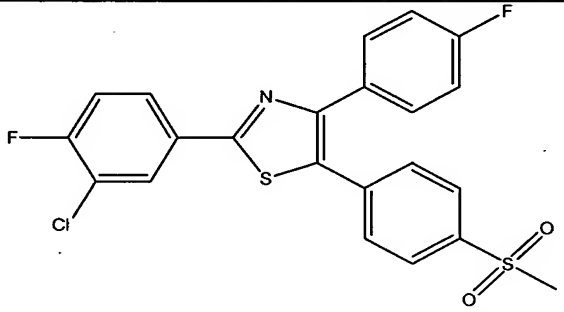
Compound Number	Structural Formula
B-94	 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-95	 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-96	 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

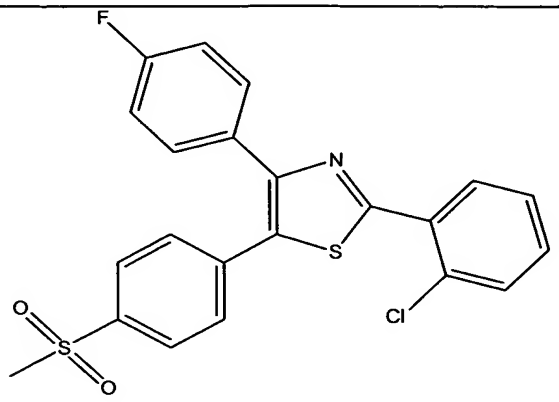
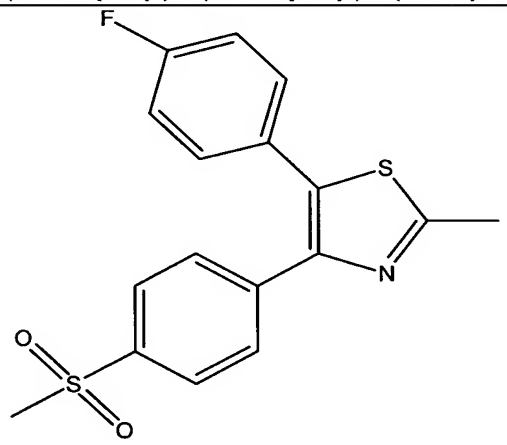
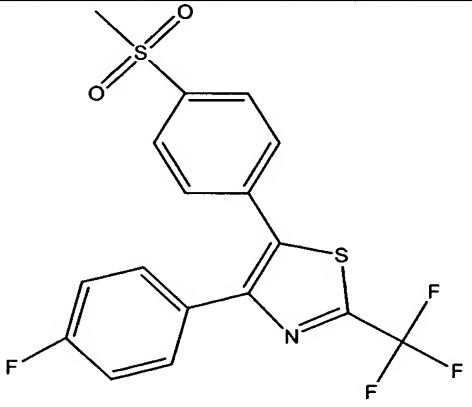
Compound Number	Structural Formula
B-97	 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-98	 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide;
B-99	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

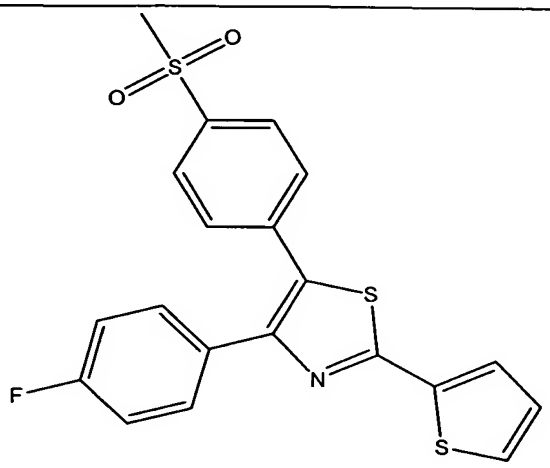
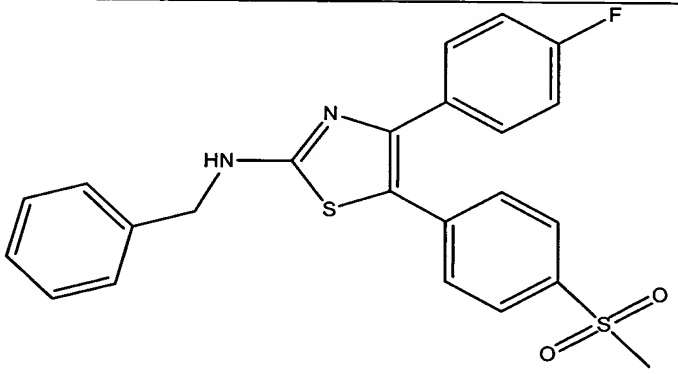
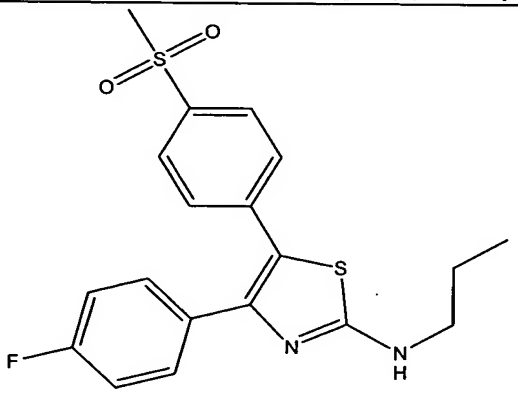
Compound Number	Structural Formula
B-100	 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-101	 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-102	 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;

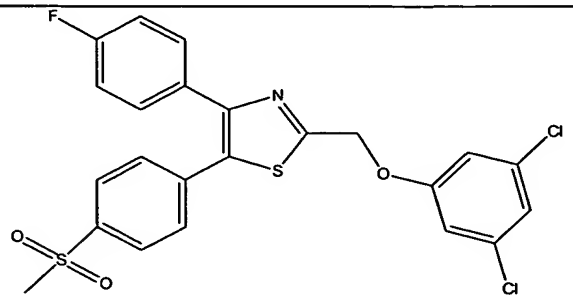
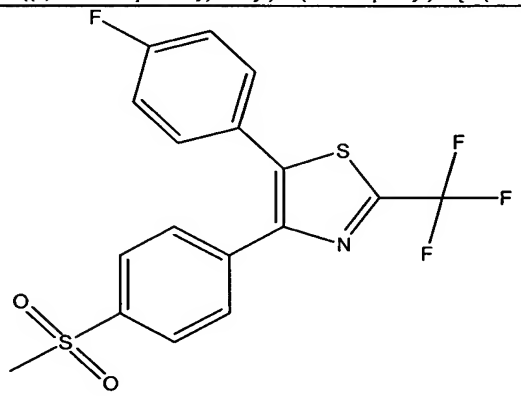
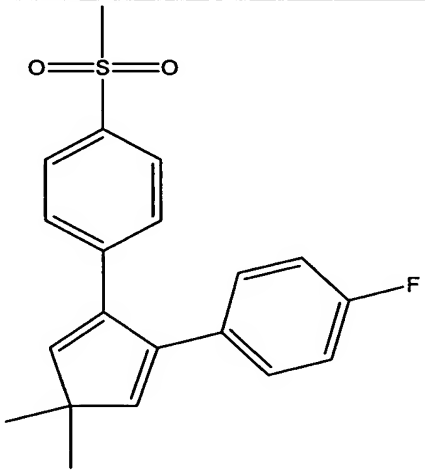
Compound Number	Structural Formula
B-103	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-104	 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-105	 6-(4-fluorophenyl)-7-[4-methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

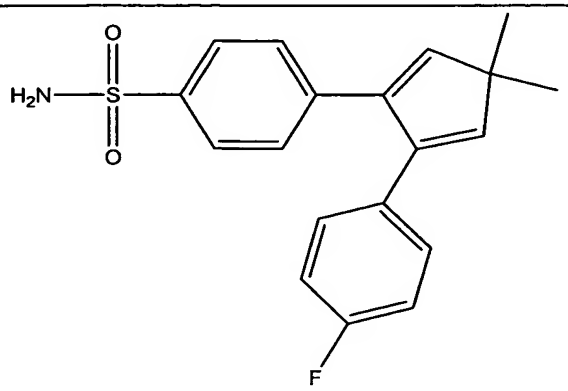
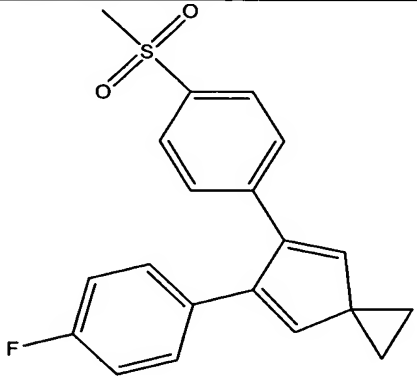
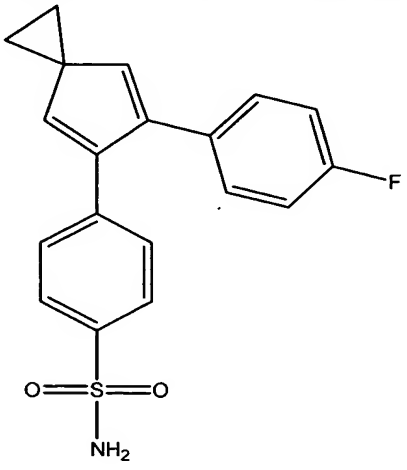
Compound Number	Structural Formula
B-106	 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-107	 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-108	 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene;

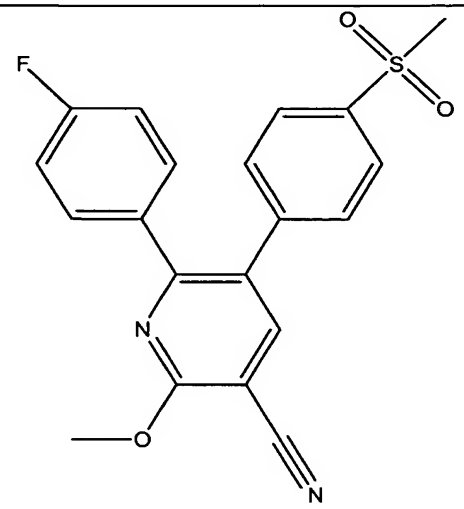
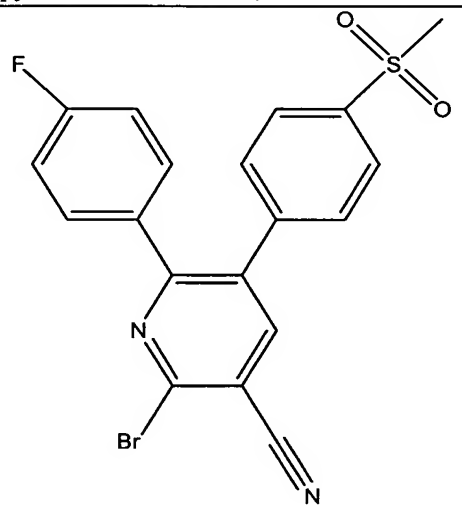
Compound Number	Structural Formula
B-109	 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-110	 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-111	 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

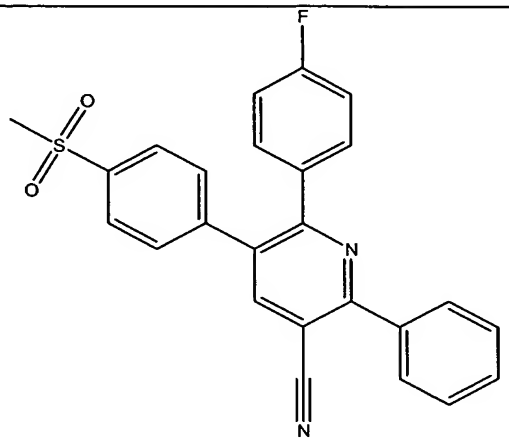
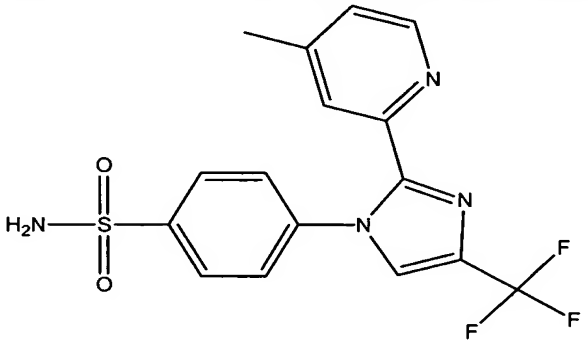
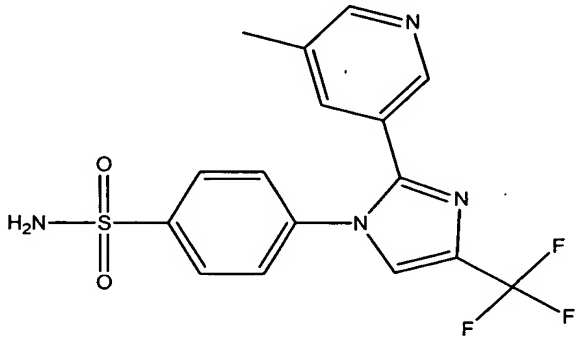
Compound Number	Structural Formula
B-112	 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
B-113	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
B-114	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

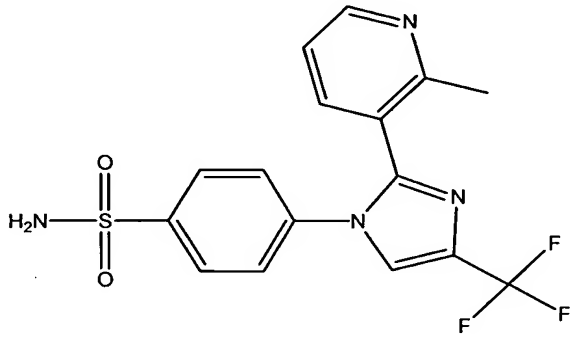
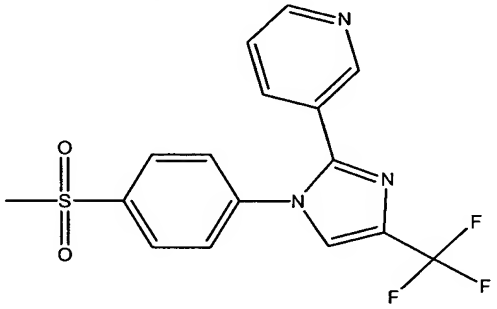
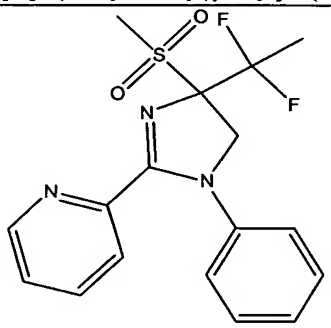
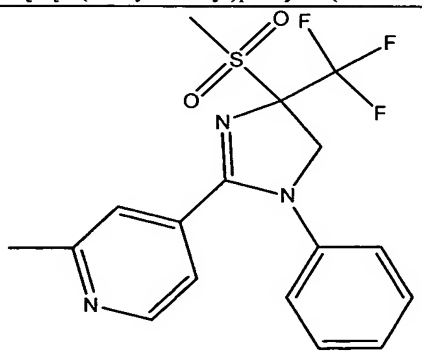
Compound Number	Structural Formula
B-115	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
B-116	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
B-117	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

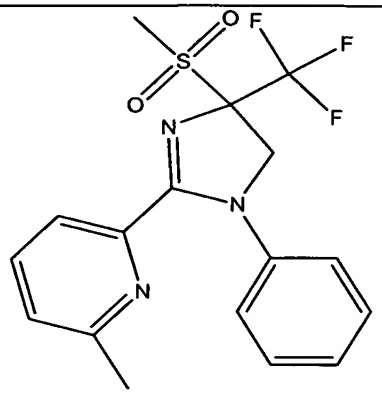
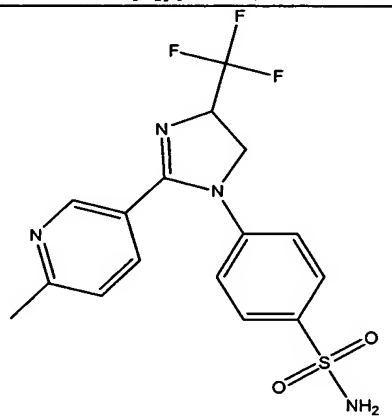
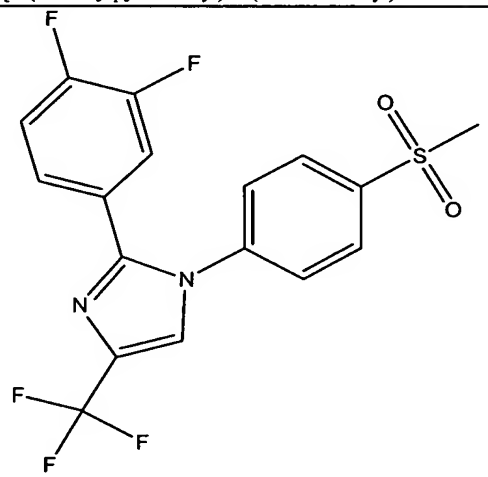
Compound Number	Structural Formula
B-118	 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;
B-119	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
B-120	 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl) cyclopenta-2,4-dien-3-yl]benzene;

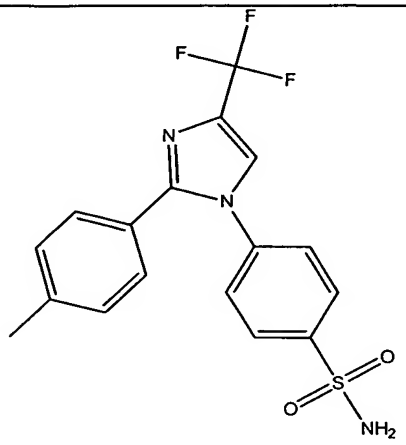
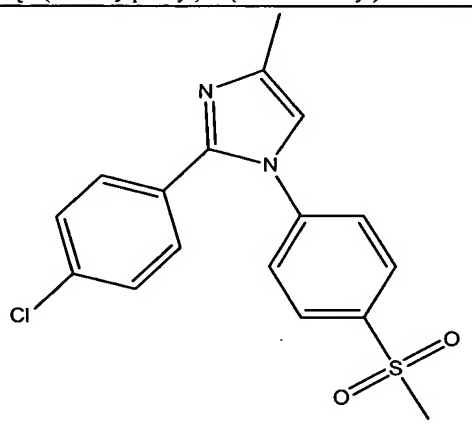
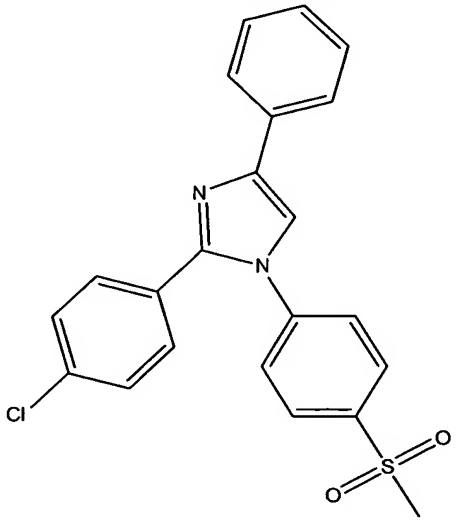
Compound Number	Structural Formula
B-121	 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide;
B-122	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
B-123	 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

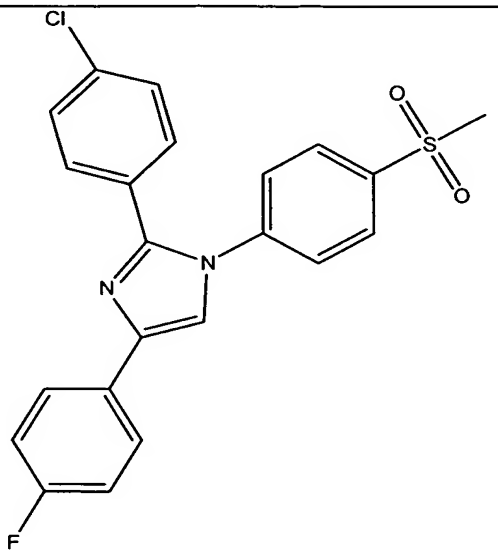
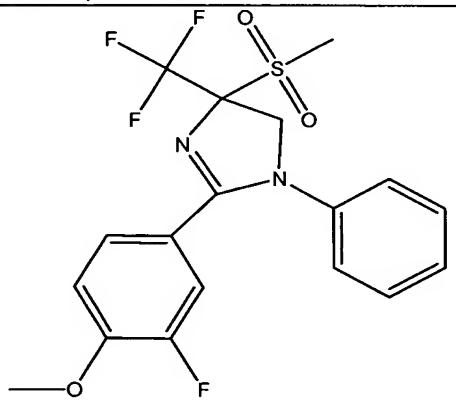
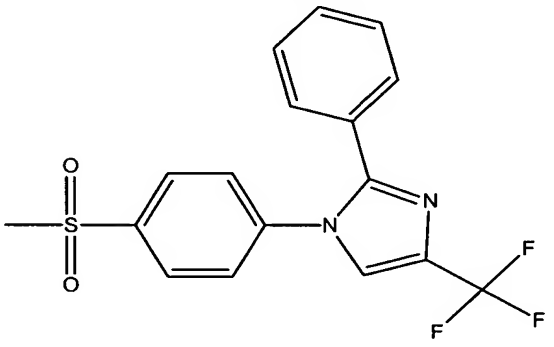
Compound Number	Structural Formula
B-124	 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;
B-125	 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;

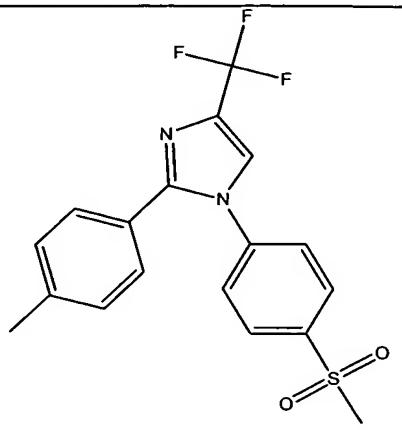
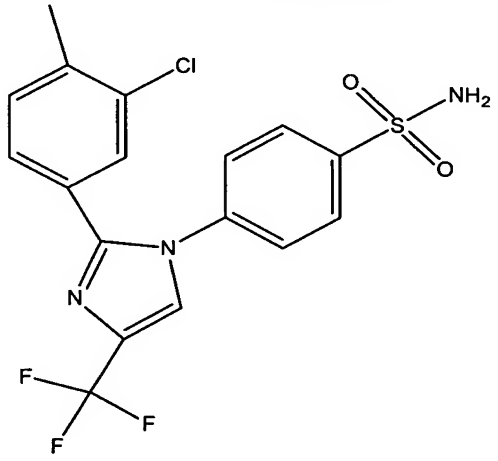
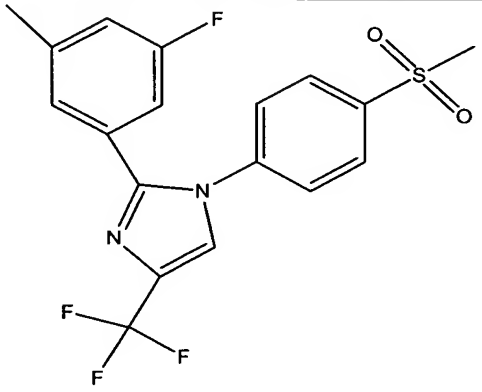
Compound Number	Structural Formula
B-126	 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;
B-127	 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-128	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;

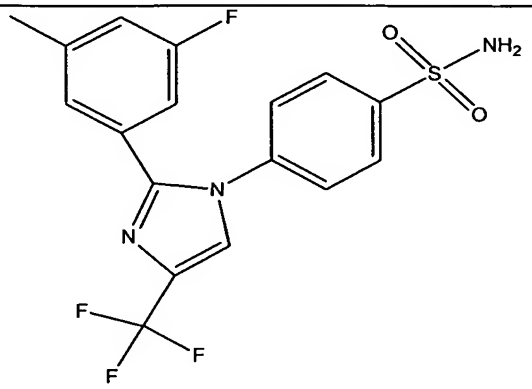
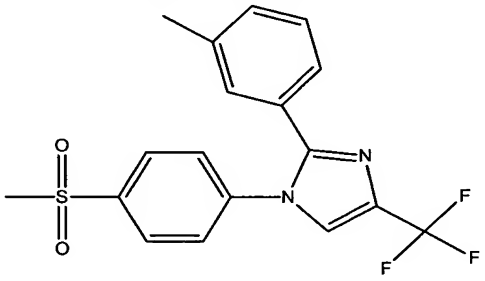
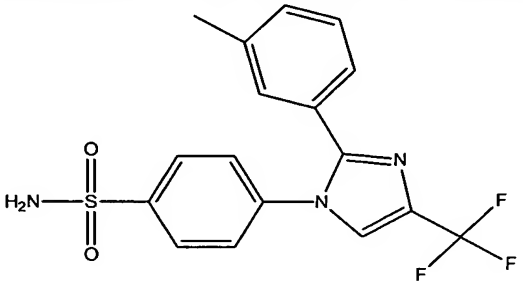
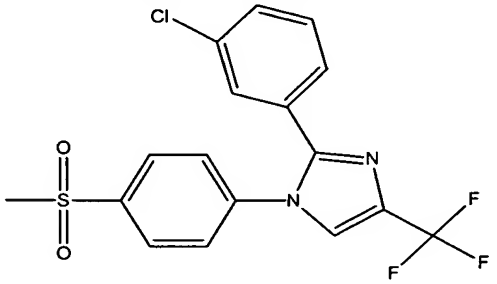
Compound Number	Structural Formula
B-129	 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-130	 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
B-131	 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;
B-132	 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;

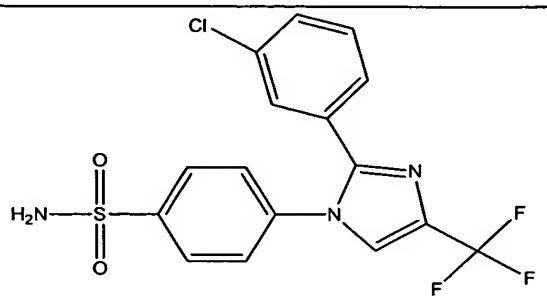
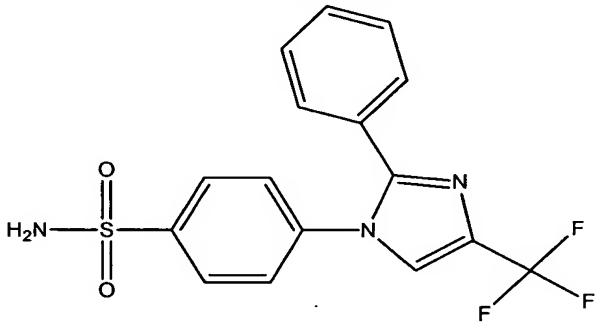
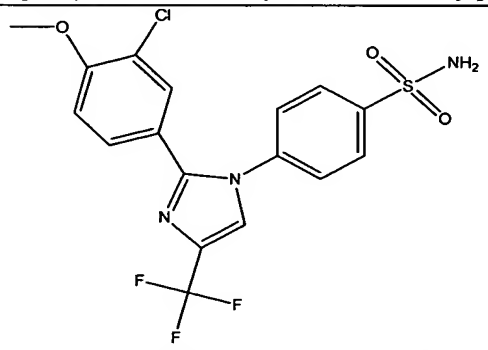
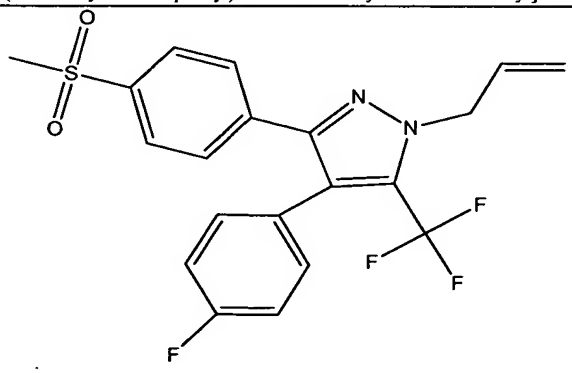
Compound Number	Structural Formula
B-133	 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;
B-134	 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-135	 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;

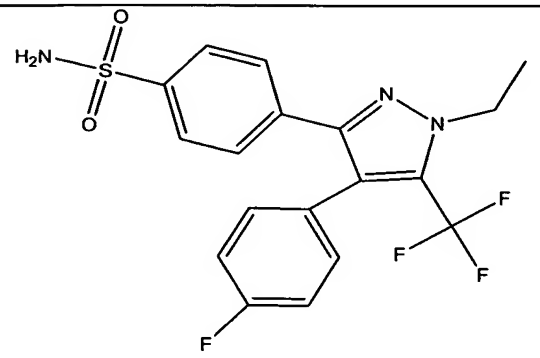
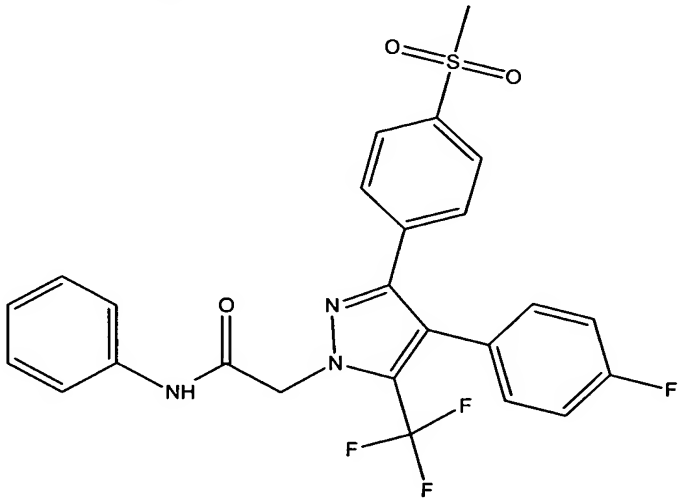
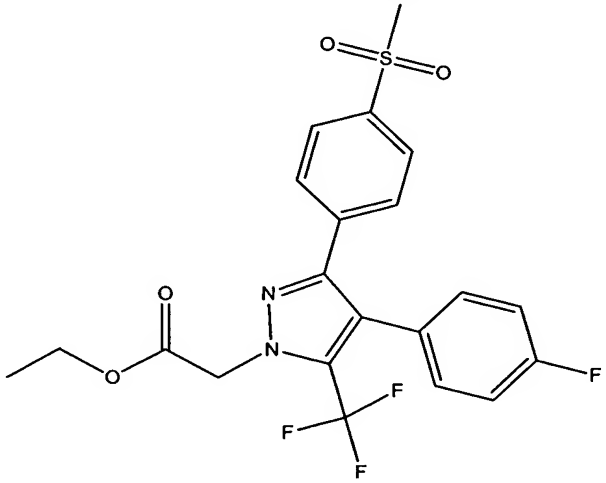
Compound Number	Structural Formula
B-136	 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-137	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
B-138	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

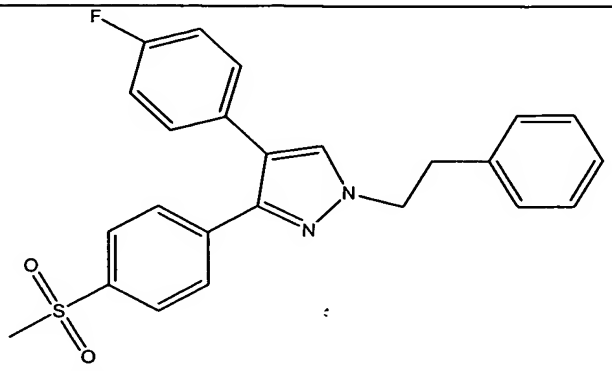
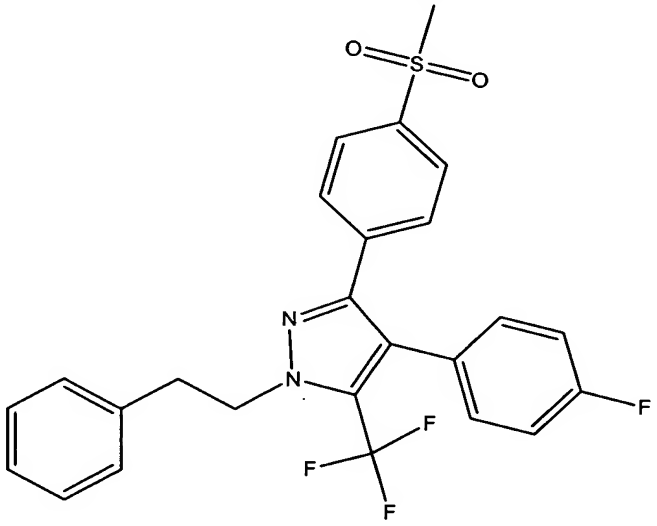
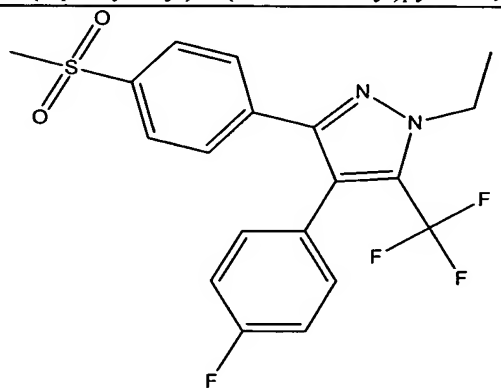
Compound Number	Structural Formula
B-139	 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl] -1H-imidazole;
B-140	 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl -4-(trifluoromethyl)]-1H-imidazole;
B-141	 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

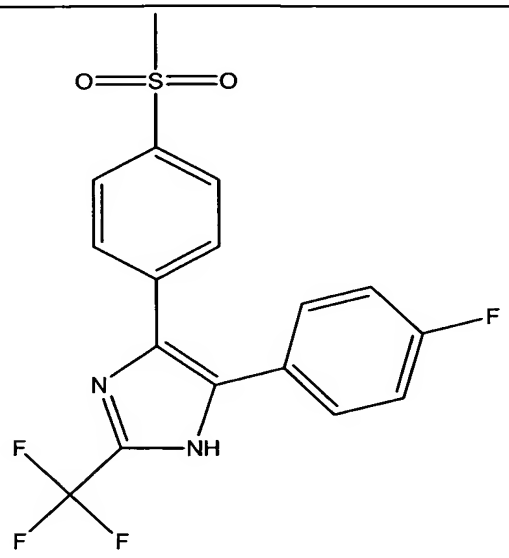
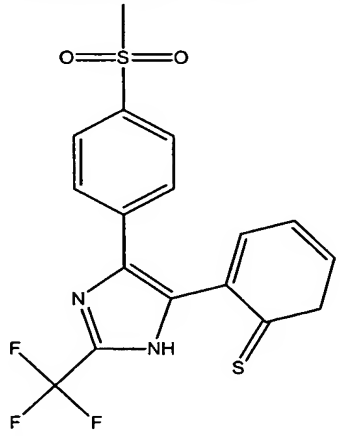
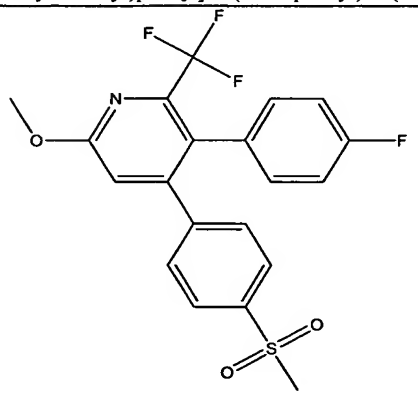
Compound Number	Structural Formula
B-142	 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
B-143	 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-144	 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;

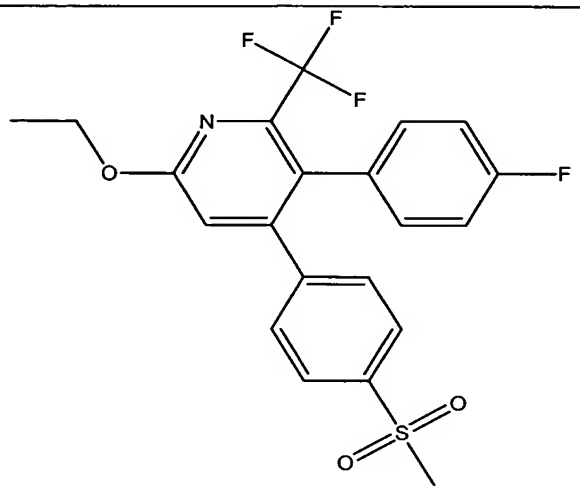
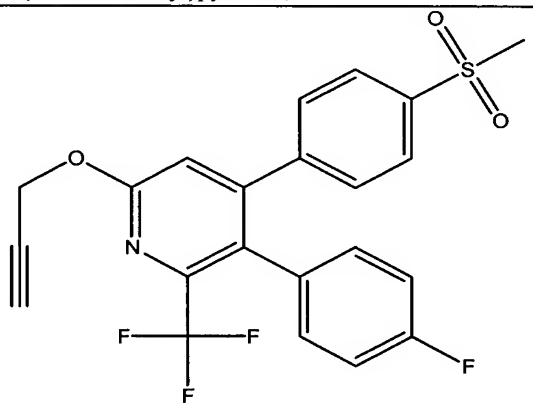
Compound Number	Structural Formula
B-145	 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl -1H-imidazole-1-yl]benzenesulfonamide;
B-146	 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
B-147	 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-148	 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole

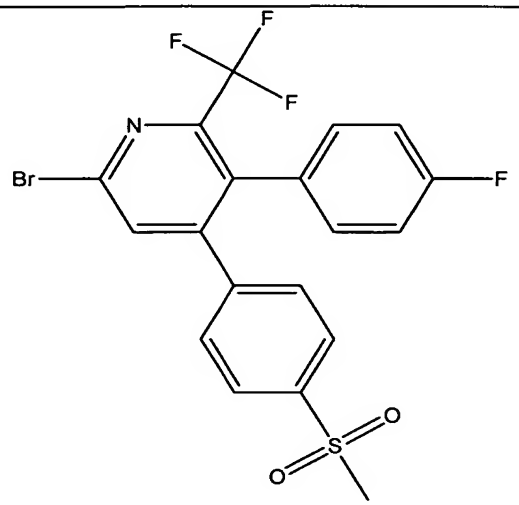
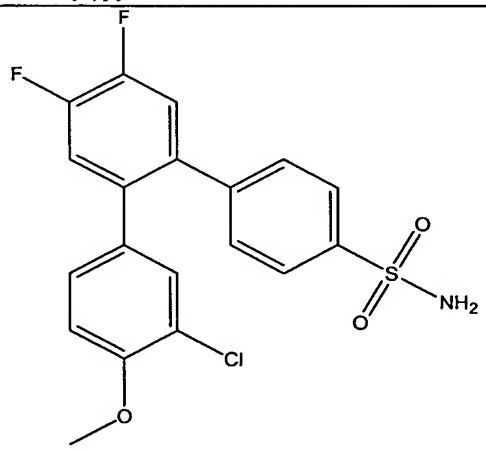
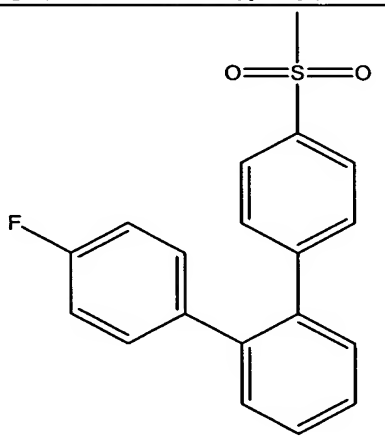
Compound Number	Structural Formula
B-149	 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-150	 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-151	 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-152	 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

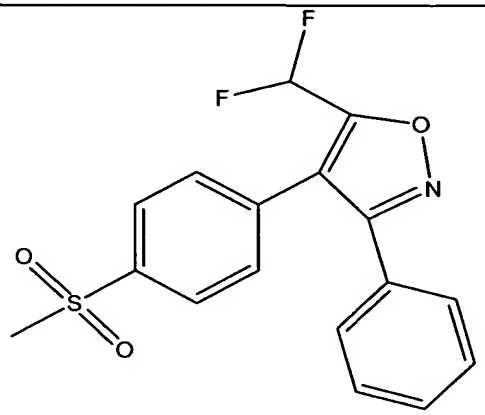
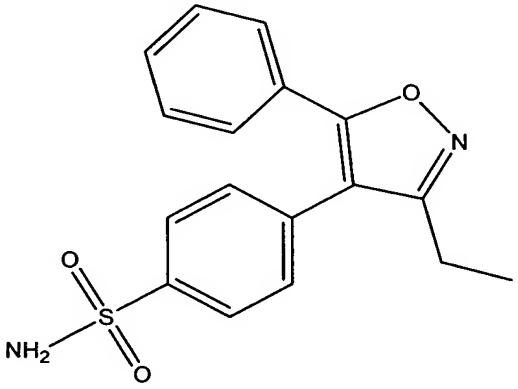
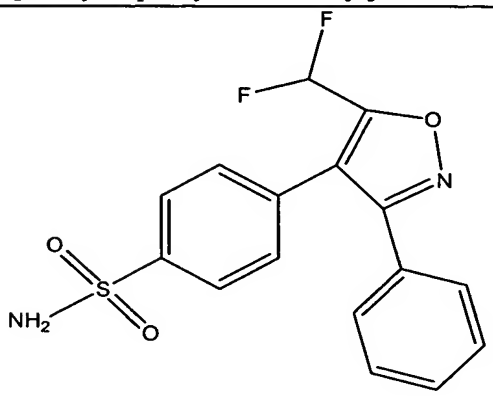
Compound Number	Structural Formula
B-153	 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide;
B-154	 N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
B-155	 ethyl[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

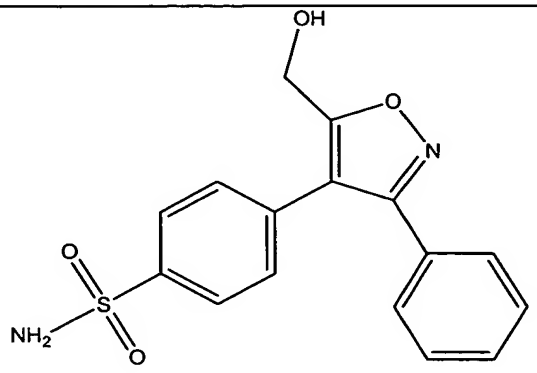
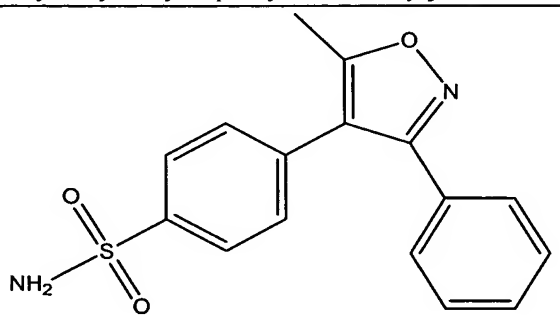
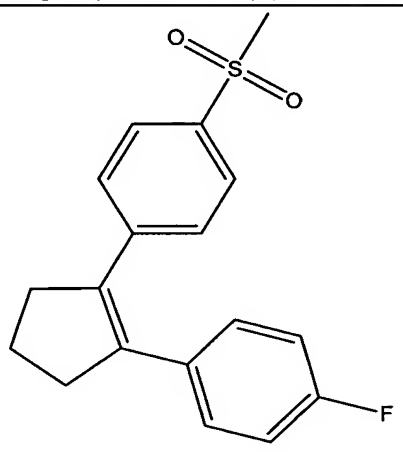
Compound Number	Structural Formula
B-156	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
B-157	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
B-158	 1-ethyl-4-(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

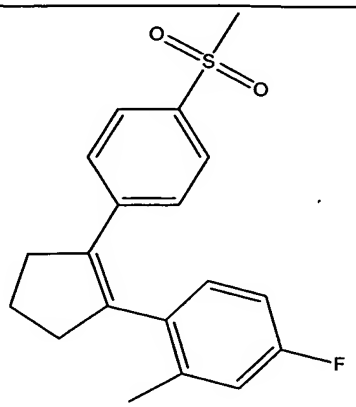
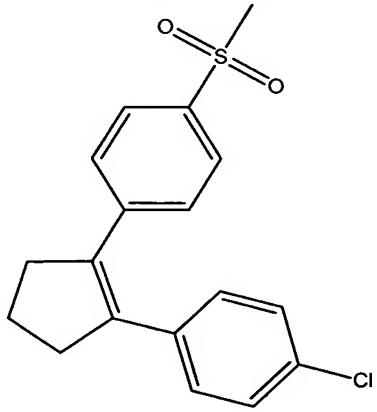
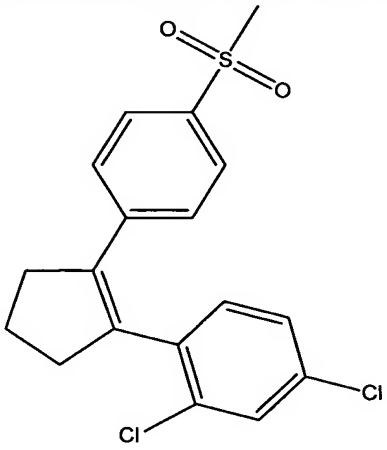
Compound Number	Structural Formula
B-159	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl) -2-trifluoromethyl-1H-imidazole;
B-160	 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
B-161	 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

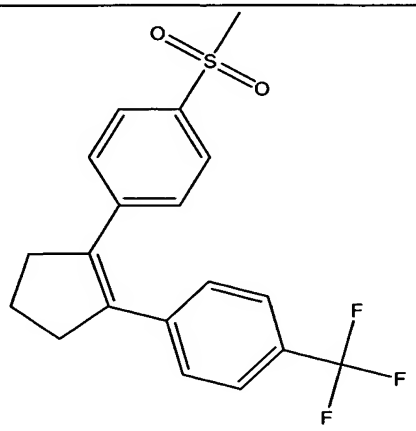
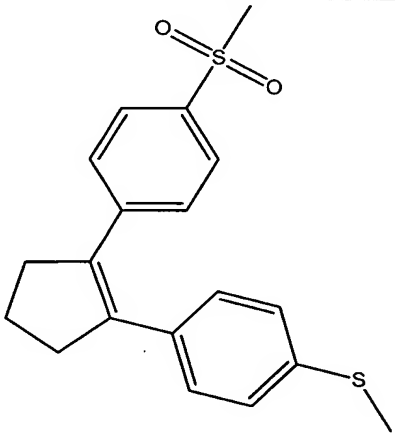
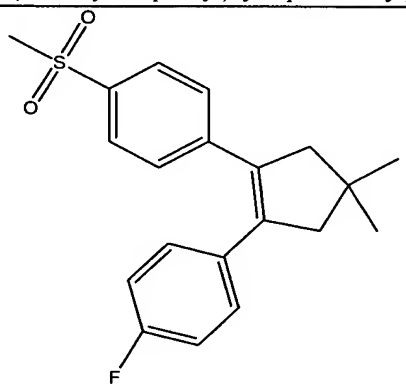
Compound Number	Structural Formula
B-162	 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;
B-163	 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

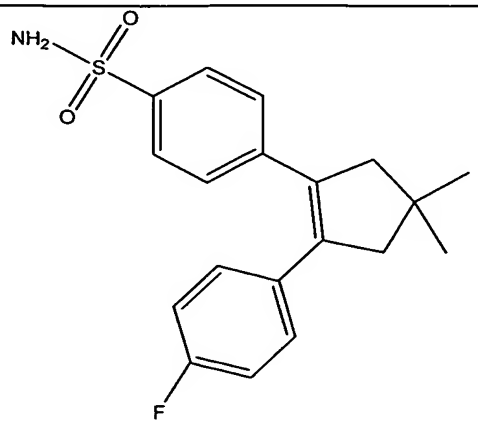
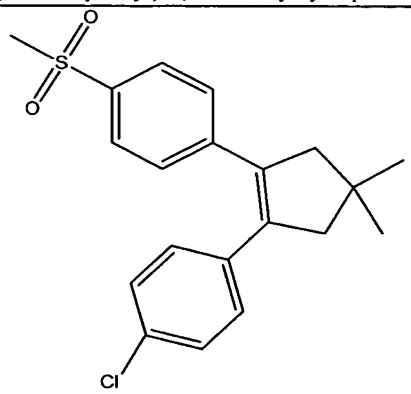
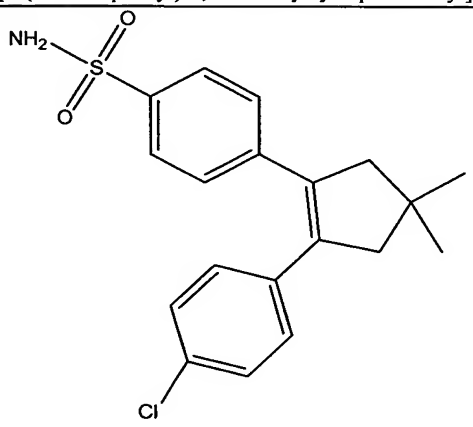
Compound Number	Structural Formula
B-164	 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;
B-165	 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
B-166	 1-(4-fluorophenyl)-2-[4-methylsulfonyl)phenyl]benzene;

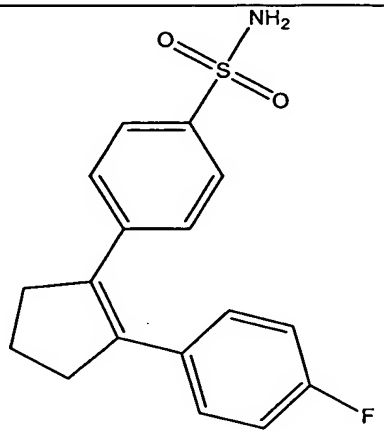
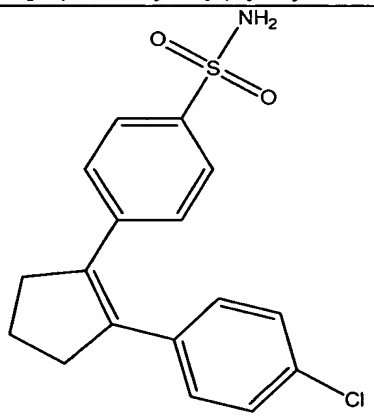
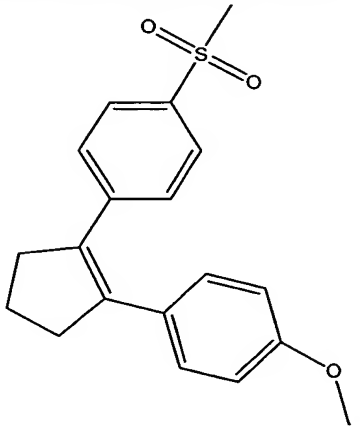
Compound Number	Structural Formula
B-167	 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;
B-168	 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
B-169	 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

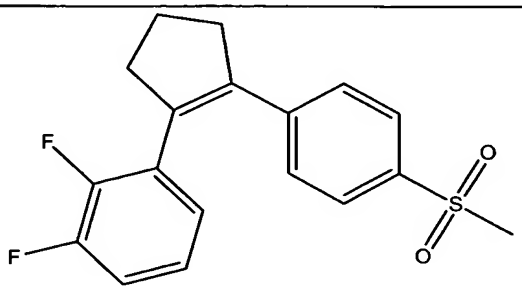
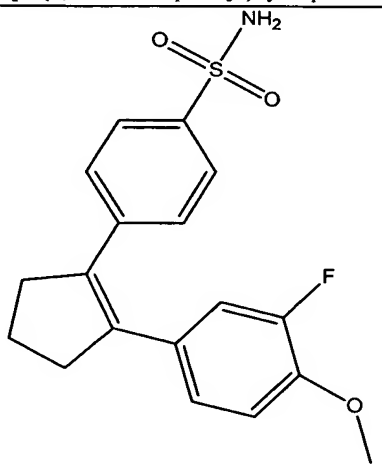
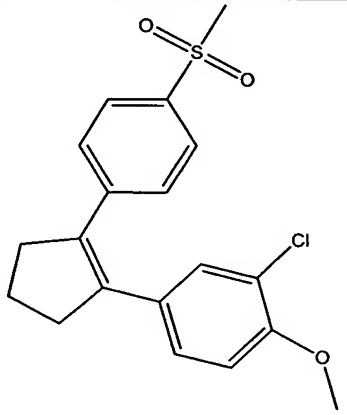
Compound Number	Structural Formula
B-170	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-171	 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
B-172	 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

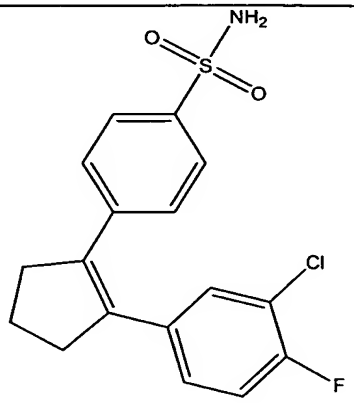
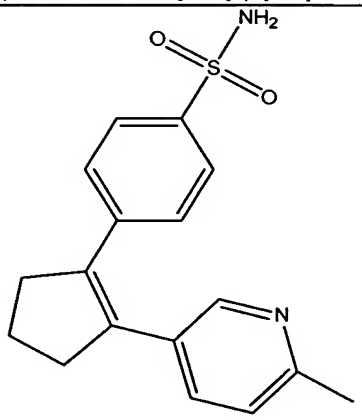
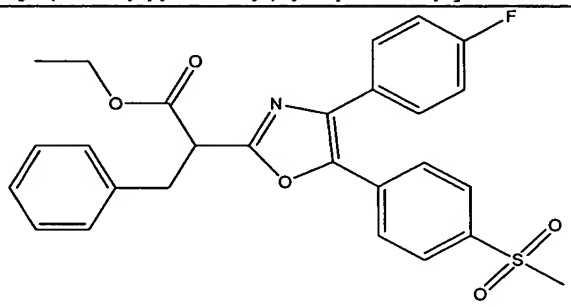
Compound Number	Structural Formula
B-173	 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-174	 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-175	 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

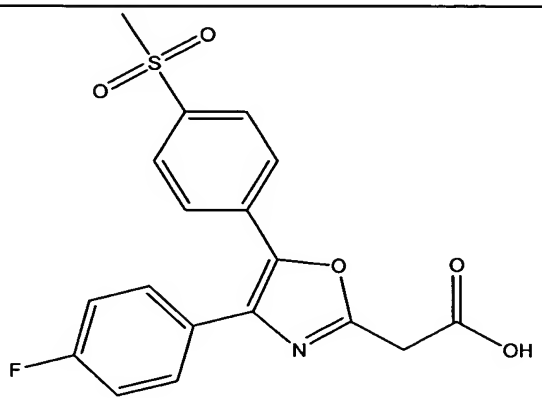
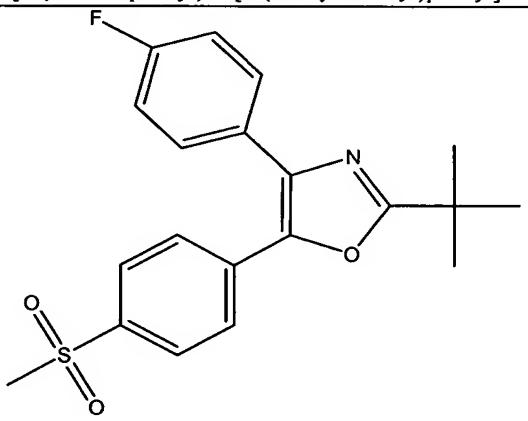
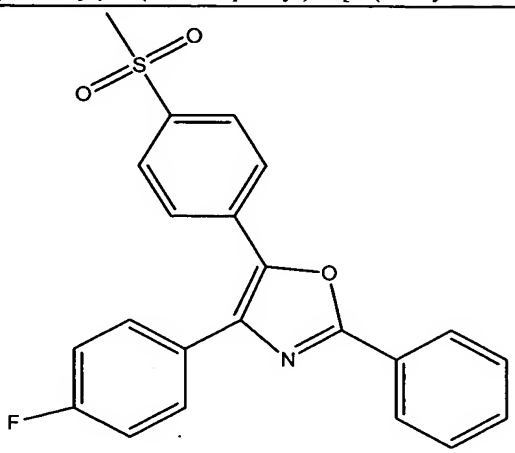
Compound Number	Structural Formula
B-176	 1-[2-(4-trifloromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-177	 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-178	 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

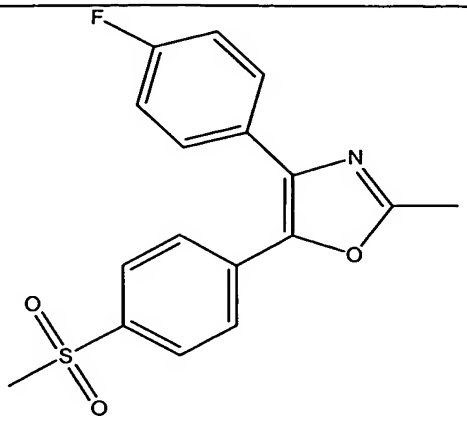
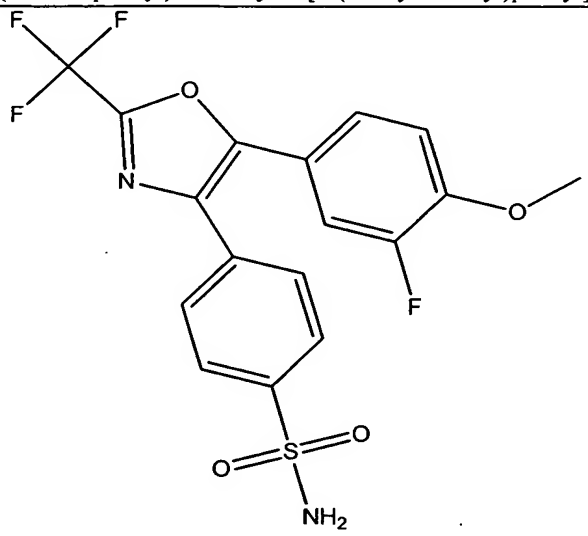
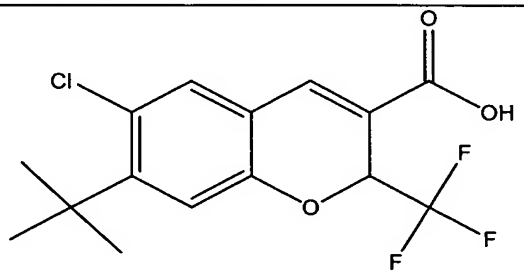
Compound Number	Structural Formula
B-179	 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
B-180	 1-[2-(3-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-181	 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

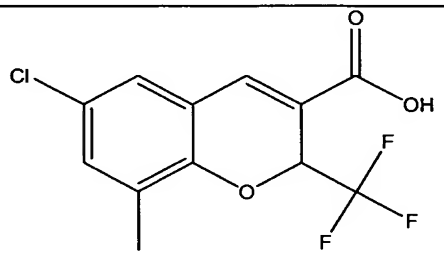
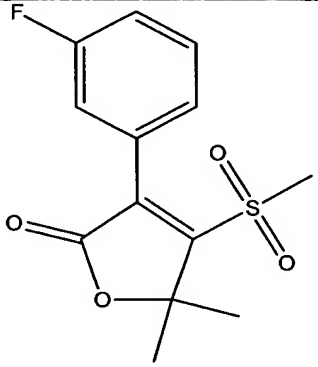
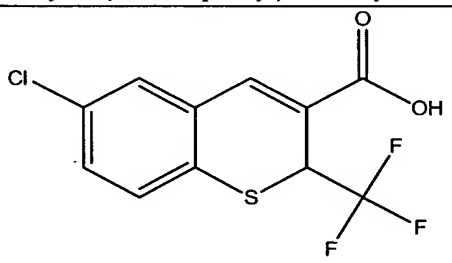
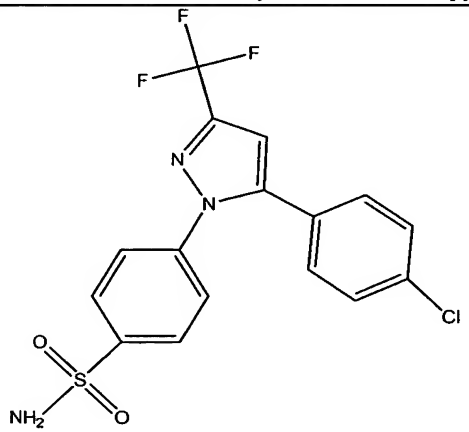
Compound Number	Structural Formula
B-182	 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-183	 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-184	 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

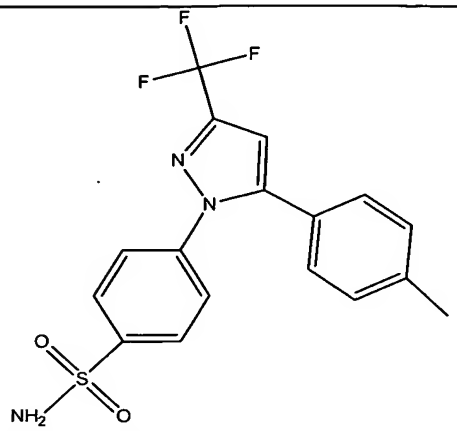
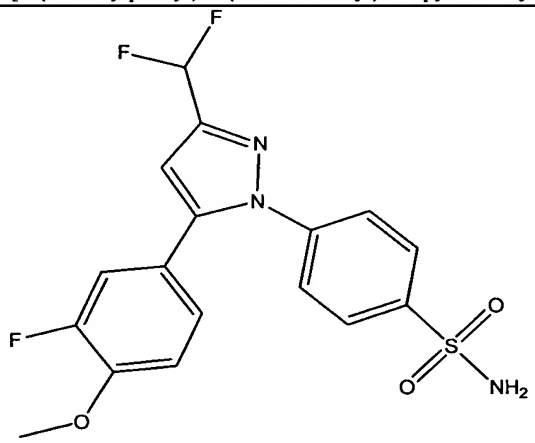
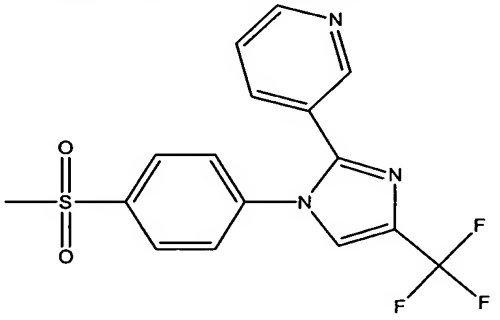
Compound Number	Structural Formula
B-185	 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-186	 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
B-187	 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

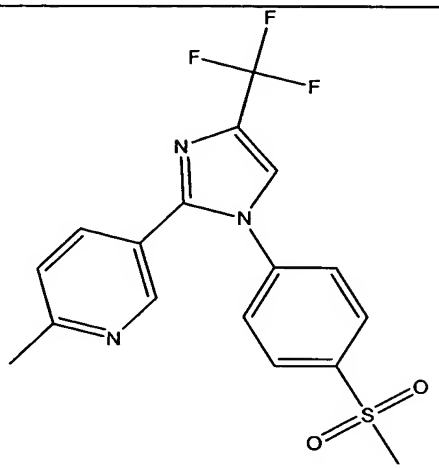
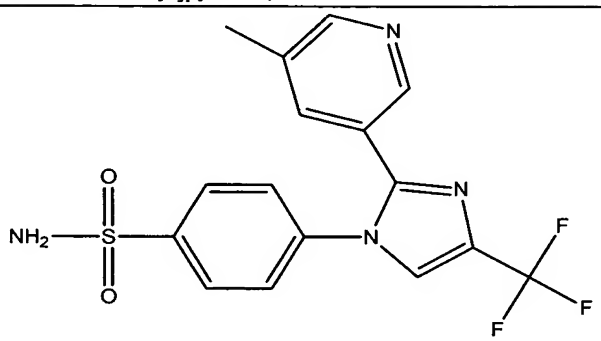
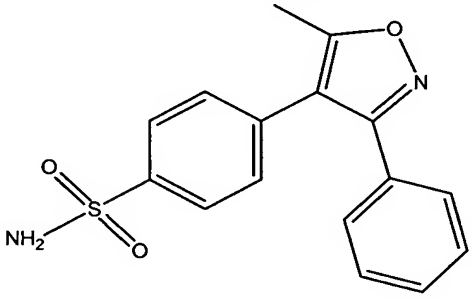
Compound Number	Structural Formula
B-188	 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-189	 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
B-190	 ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;

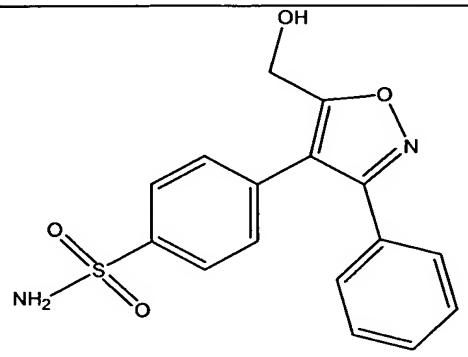
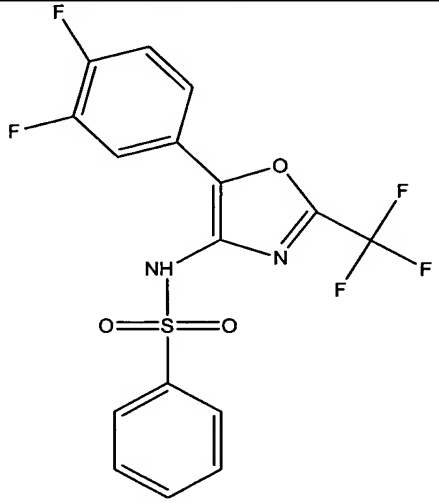
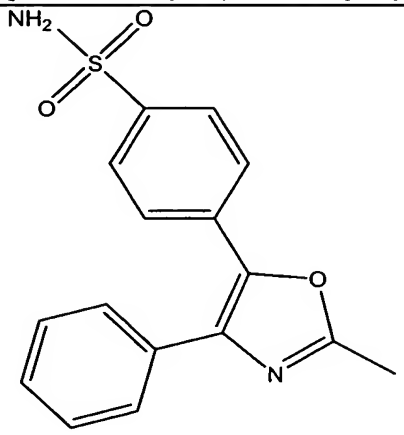
Compound Number	Structural Formula
B-191	 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;
B-192	 2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
B-193	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

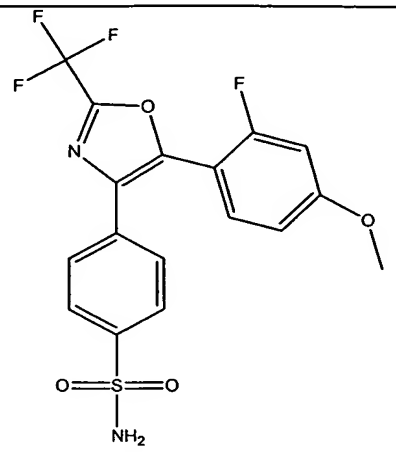
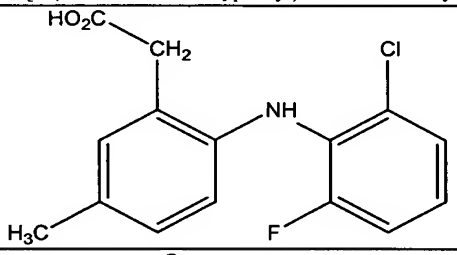
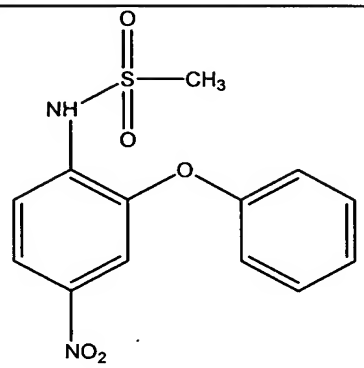
Compound Number	Structural Formula
B-194	 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
B-195	 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl -4-oxazolyl]benzenesulfonamide;
B-196	 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H -1-benzopyran-3-carboxylic acid;

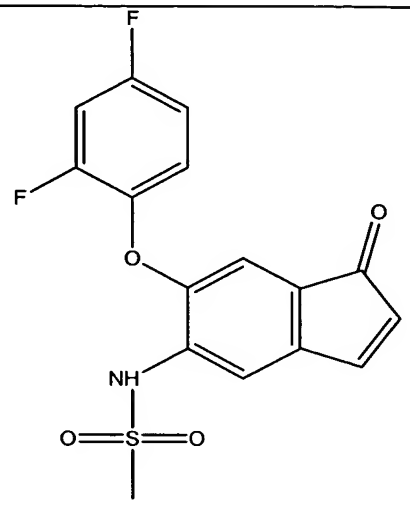
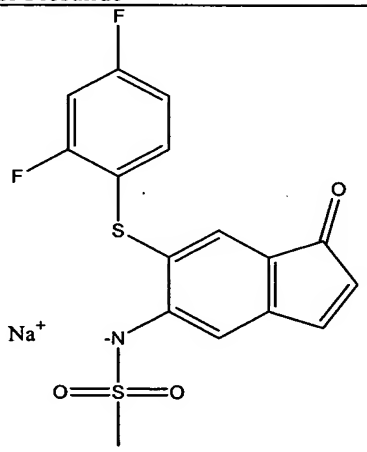
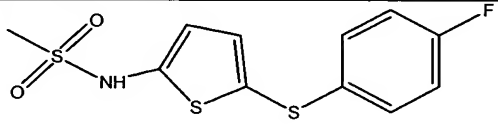
Compound Number	Structural Formula
B-197	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-198	 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone;
B-199	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
B-200	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

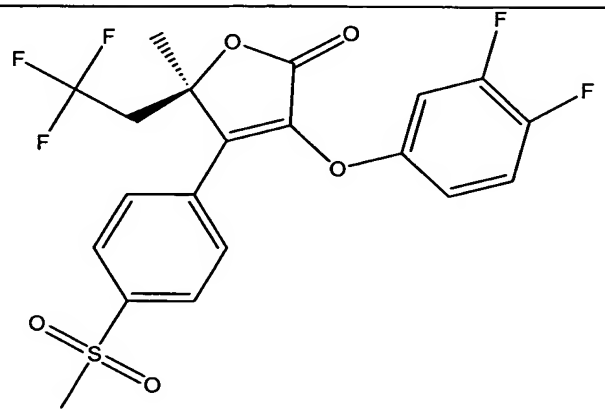
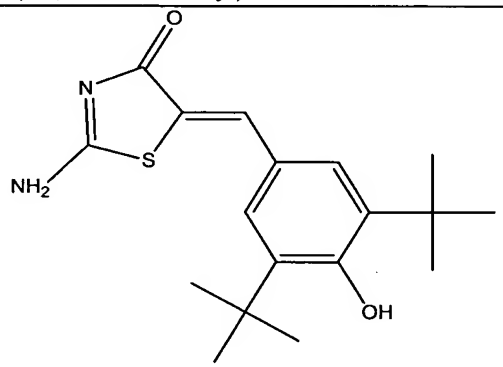
Compound Number	Structural Formula
B-201	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-202	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;
B-203	 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

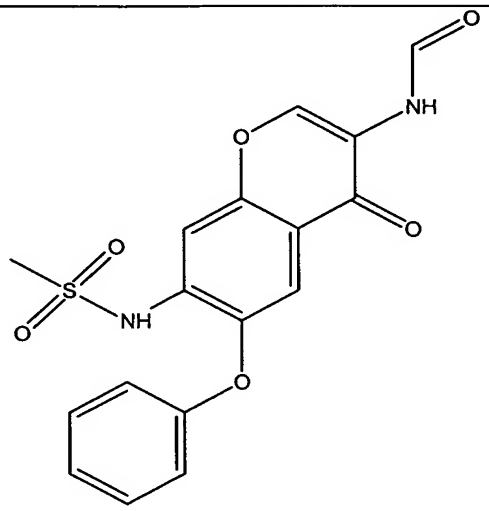
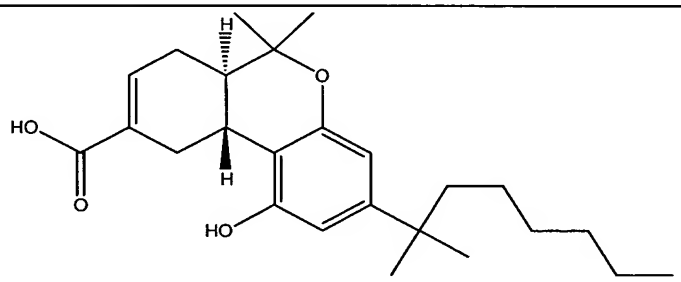
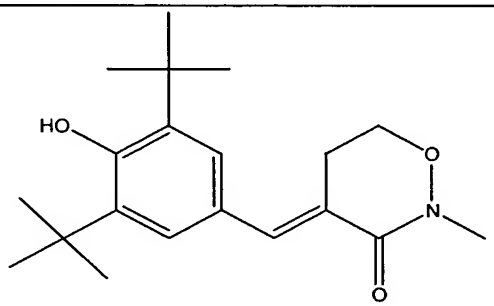
Compound Number	Structural Formula
B-204	 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl -1H-imidazol-2-yl]pyridine;
B-205	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-206	 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

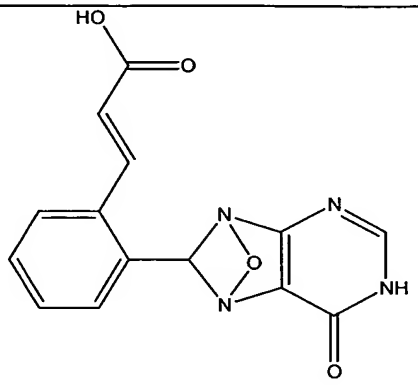
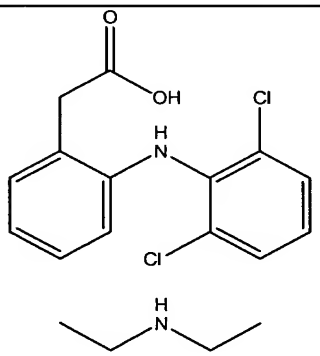
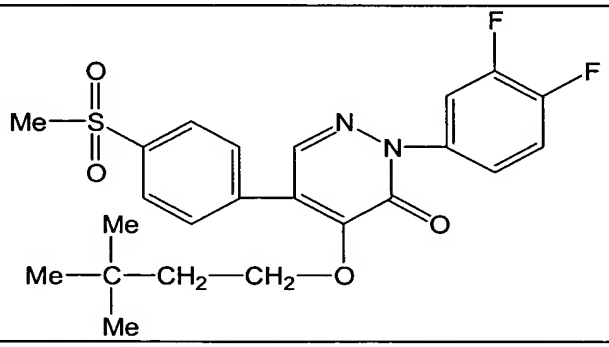
Compound Number	Structural Formula
B-207	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-208	 [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
B-209	 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;

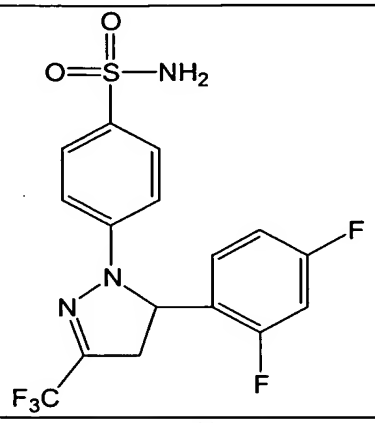
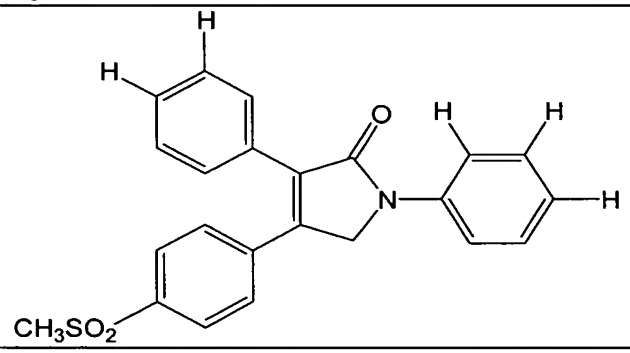
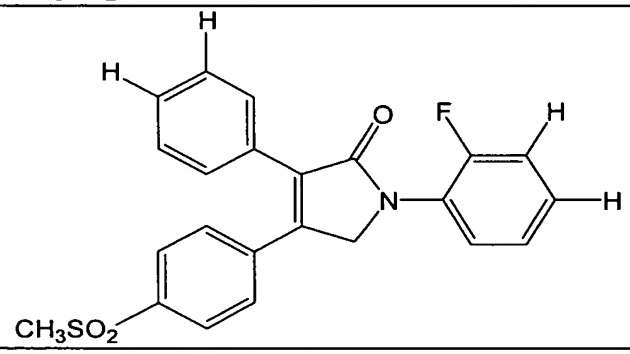
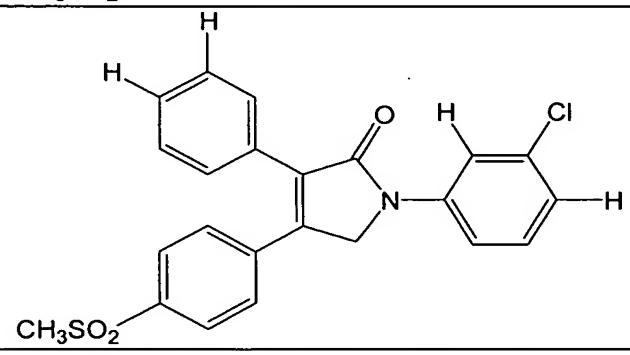
Compound Number	Structural Formula
B-210	 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
B-211	
B-212	 *N*-(4-nitro-2-phenoxy-phenyl)-methanesulfonamide or Nimesulide

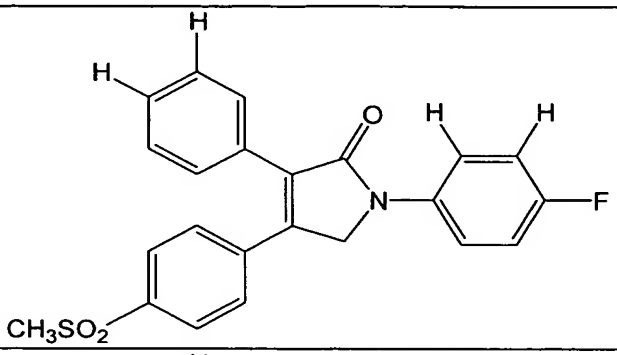
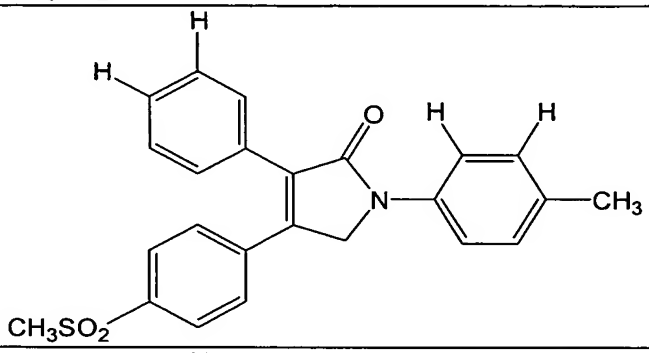
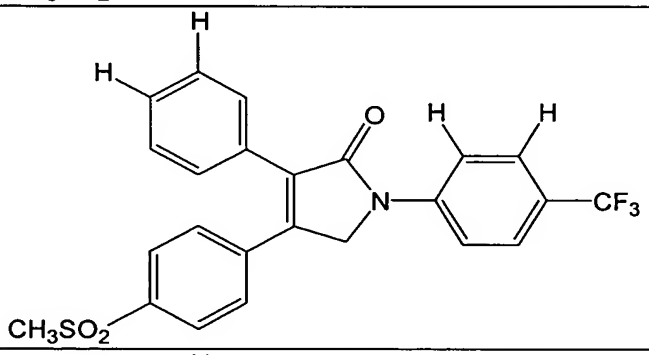
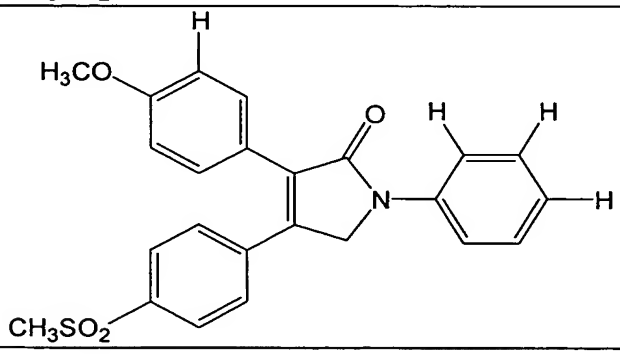
Compound Number	Structural Formula
B-213	 N-[6-(2,4-difluoro-phenoxy)-1-oxo-inden-5-yl]-methanesulfonamide or Flosulide
B-214	 *N*-[6-(2,4-difluoro-phenylsulfanyl)-1-oxo-1*H*-inden-5-yl]-methanesulfonamide, soldium salt, or L-745337
B-215	 N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide or RWJ-63556

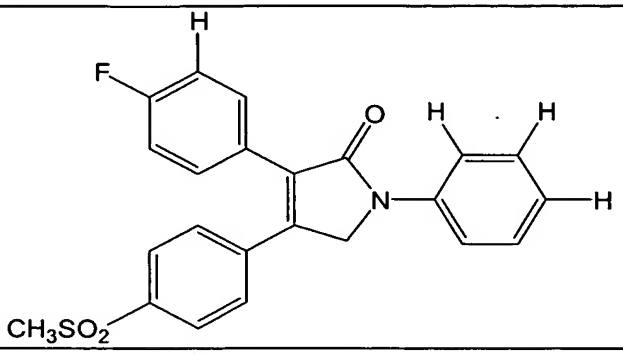
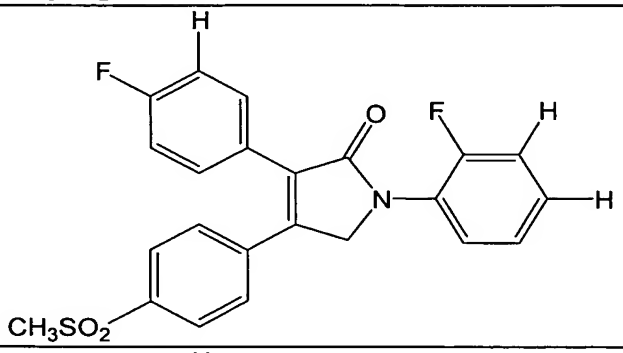
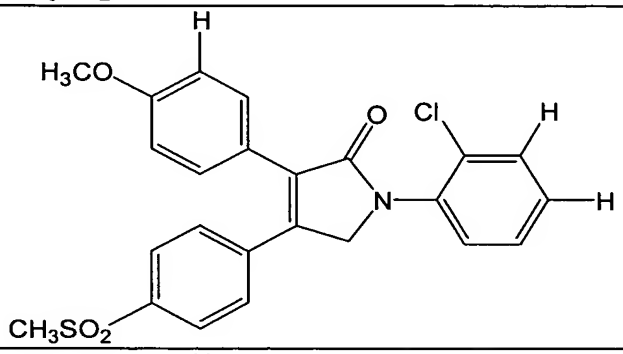
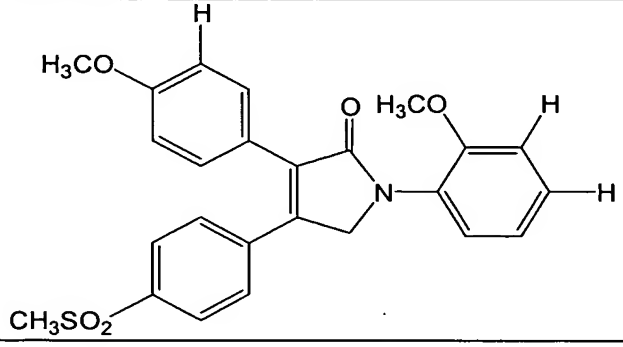
Compound Number	**Structural Formula**
B-216	 3-(3,4-difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl -5-(2,2,2-trifluoro-ethyl)-5*H*-furan-2-one or L-784512
B-217	 (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] -4(5H)-thiazolone or Darbufelone
B-218	CS-502
B-219	LAS-34475
B-220	LAS-34555
B-221	S-33516
B-222	SD-8381
B-223	L-783003

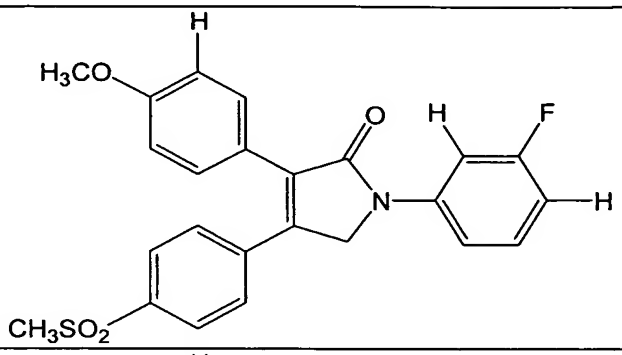
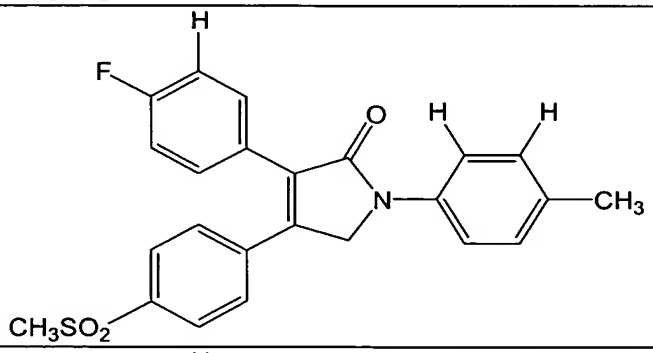
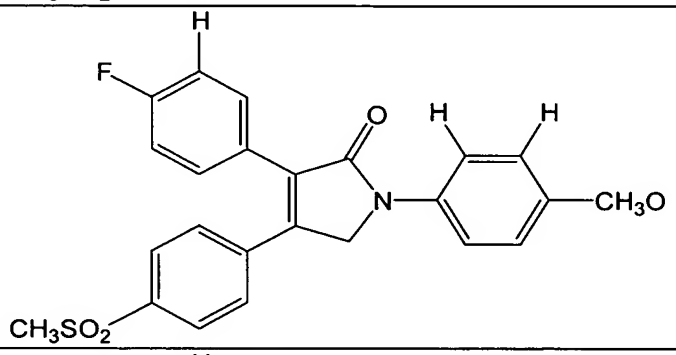
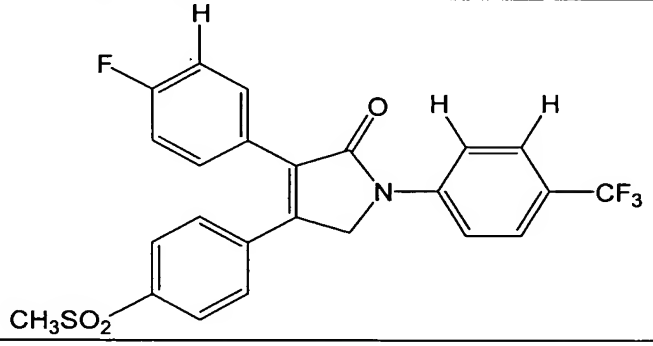
Compound Number	**Structural Formula**
B-224	 N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] -methanesulfonamide or T614
B-225	D-1367
B-226	L-748731
B-227	 (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethy 1-6H-dibenzo[b,d]pyran-9-carboxylic acid or CT3
B-228	CGP-28238
B-229	 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389

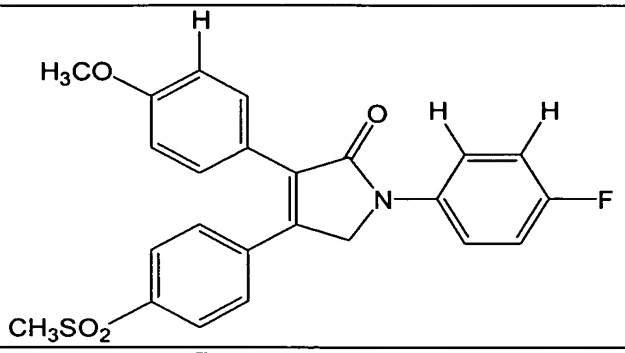
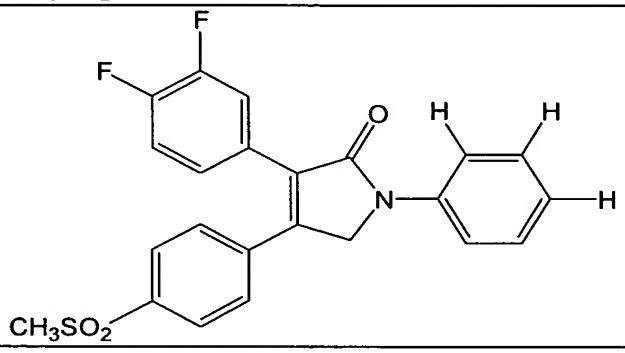
Compound Number	**Structural Formula**
B-230	GR-253035
B-231	 2-(6-dioxo-9H-purin-8-yl)cinnamic acid
B-232	S-2474
B-233	
B-234	

Compound Number	Structural Formula
B-235	
B-236	
B-237	
B-238	

Compound Number	Structural Formula
B-239	
B-240	
B-241	
B-242	

Compound Number	**Structural Formula**
B-243	
B-244	
B-245	
B-246	

Compound Number	**Structural Formula**
B-247	
B-248	
B-249	
B-250	

Compound Number	Structural Formula
B-251	
B-252	

[0376] The cyclooxygenase-2 selective inhibitor employed in the present invention can exist in tautomeric, geometric or stereoisomeric forms. Generally speaking, suitable cyclooxygenase-2 selective inhibitors that are in tautomeric, geometric or stereoisomeric forms are those compounds that inhibit cyclooxygenase-2 activity by about 25%, more typically by about 50%, and even more typically, by about 75% or more when present at a concentration of 100 μM or less. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the invention. The terms "cis" and "trans", as used herein, denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans"). Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms. Furthermore, some of the compounds described contain one or more

stereocenters and are meant to include R, S, and mixtures or R and S forms for each stereocenter present.

[0377] The cyclooxygenase-2 selective inhibitors utilized in the present invention may be in the form of free bases or pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically-acceptable salts" are salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt may vary, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds for use in the present methods may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of use in the present methods include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound of any Formula set forth herein.

[0378] The cyclooxygenase-2 selective inhibitors of the present invention can be formulated into pharmaceutical compositions and administered by a number of different means that will deliver a therapeutically effective dose. Such compositions can be administered orally, parenterally, by inhalation spray, rectally, intradermally, transdermally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants,

and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania (1975), and Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y. (1980).

[0379] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

[0380] Suppositories for rectal administration of the compounds discussed herein can be prepared by mixing the active agent with a suitable non-irritating excipient such as cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature, and which will therefore melt in the rectum and release the drug.

[0381] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium

and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

[0382] For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

[0383] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0384] The amount of active ingredient that can be combined with the carrier materials to produce a single dosage of the cyclooxygenase-2 selective inhibitor will vary depending upon the patient and the particular mode of administration. In general, the pharmaceutical compositions may contain a cyclooxygenase-2 selective inhibitor in the range of about 0.1 to 2000 mg, more typically, in the range of about 0.5 to 500 mg and still more typically, between about 1 and 200 mg. A daily dose of about 0.01 to 100 mg/kg body weight, or more typically, between about 0.1 and about 50 mg/kg body weight and even more typically, from about 1 to 20 mg/kg body weight, may be appropriate. The daily dose is generally administered in one to about four doses per day.

[0385] In one embodiment, when the cyclooxygenase-2 selective inhibitor comprises rofecoxib, it is typical that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more typically, from about 0.18 to about 0.4 mg/day·kg.

[0386] In still another embodiment, when the cyclooxygenase-2 selective inhibitor comprises etoricoxib, it is typical that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0387] Further, when the cyclooxygenase-2 selective inhibitor comprises celecoxib, it is typical that the amount used is within a range of from about 1 to about 20 mg/day·kg, even more typically, from about 1.4 to about 8.6 mg/day·kg, and yet more typically, from about 2 to about 3 mg/day·kg.

[0388] When the cyclooxygenase-2 selective inhibitor comprises valdecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0389] In a further embodiment, when the cyclooxygenase-2 selective inhibitor comprises parecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 1 to about 3 mg/day·kg.

[0390] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

POTASSIUM ION CHANNEL MODULATORS

[0391] In addition to a cyclooxygenase-2 selective inhibitor, the composition of the invention also comprises a therapeutically effective amount of a potassium ion channel modulator or a pharmaceutically acceptable salt or prodrug thereof. A number of potassium ion channel modulators may be employed in the present invention. In some aspects, the potassium ion channel modulator may reverse or lessen central nervous system cell damage following a reduction in blood flow to the central nervous system. In other aspects, the

potassium ion channel modulator may reverse or lessen central nervous system cell damage following a traumatic brain or spinal cord injury.

[0392] In one aspect of the invention, the potassium ion channel modulator is a potassium ion channel blocker. In one embodiment, the potassium ion channel blocker is a voltage-gated potassium channel blocker. In one alternative of this embodiment, the potassium ion channel blocker is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, and tityustoxin K, or a pharmaceutically acceptable salt or prodrug thereof.

[0393] In another embodiment, the potassium ion channel blocker is a calcium-activated potassium channel blocker. In one alternative of this embodiment, the potassium ion channel blocker is selected from the group consisting of apamin, charylotoxin, clotrimazole, dequalinium chloride, iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, and penitrem A, or a pharmaceutically acceptable salt or prodrug thereof.

[0394] In a further embodiment, the potassium ion channel blocker is an ATP-sensitive potassium channel blocker. In one alternative of this embodiment, the potassium ion channel blocker is selected from the group consisting of tolbutamide, chlorpropamide, glibenclamide, glipizide, nateglinide, repaglinide, glyburide, and tolazamide, or a pharmaceutically acceptable salt or prodrug thereof.

[0395] In another aspect of the invention, the potassium ion channel modulator is a potassium ion channel opener. In one embodiment, the potassium ion channel opener is a voltage-gated potassium channel opener. In one alternative of this embodiment, the voltage-gated potassium channel opener is selected from the group consisting of BMS-204352, and N-[(3R,4S)-6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl]-N-methyl.

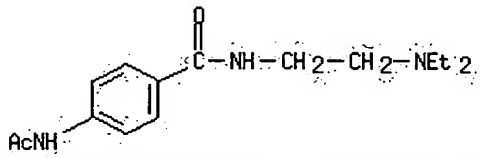
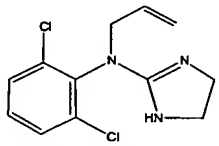
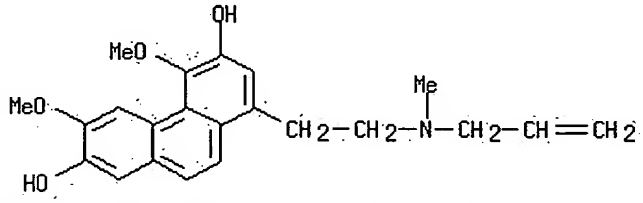
[0396] In another embodiment, the potassium ion channel opener is a calcium-activated potassium channel opener. In one alternative of this embodiment, the potassium ion channel opener is selected from the group consisting of NS1619, NS004, SCA4D, DHS-1, NS1608, Maxi-k dial, and CGS7184, or a pharmaceutically acceptable salt or prodrug thereof.

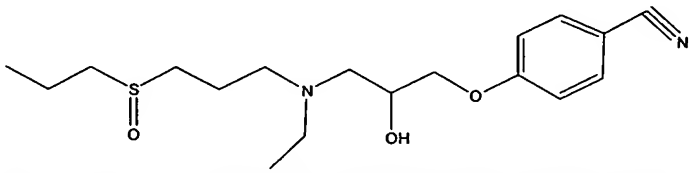
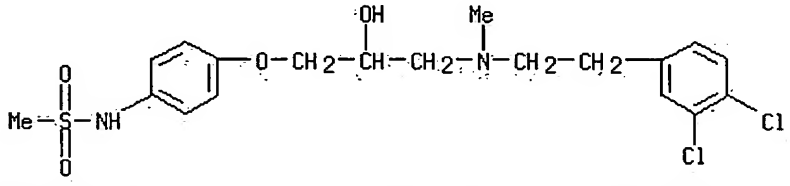
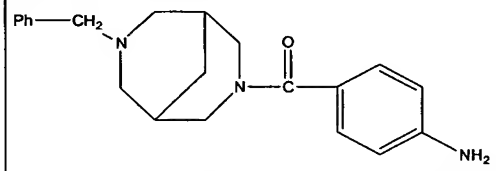
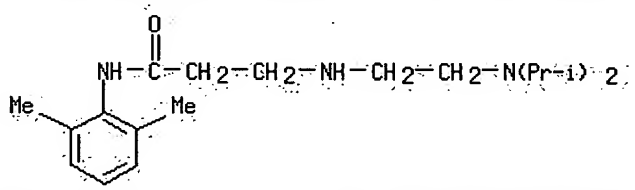
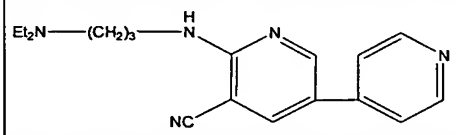
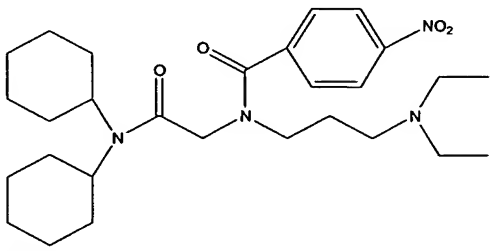
[0397] In a further embodiment, the potassium ion channel opener is an ATP-sensitive potassium channel opener. In one alternative of this embodiment, the potassium ion channel opener is selected from the group consisting of minoxidil, diazoxide, pinacidil, cromakalim, nicorandil, aprilkalim, ZD6169, bimakalim, BRL55834, levcromakalim, BMS-180448, and RP66471, or a pharmaceutically acceptable salt or prodrug thereof.

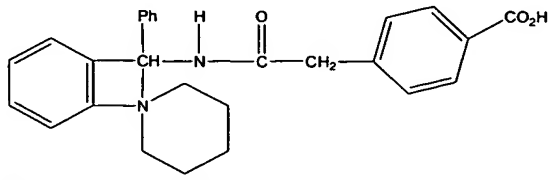
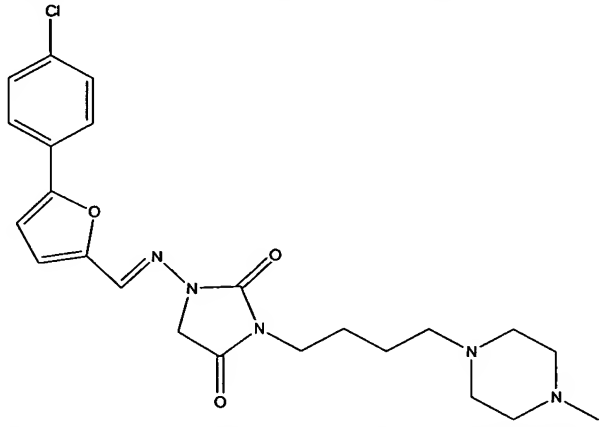
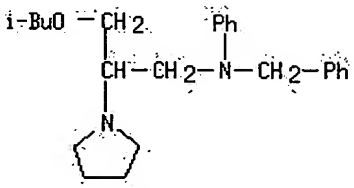
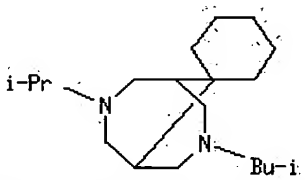
[0398] In a further embodiment, compounds that are useful for the potassium ion channel blocker or a pharmaceutically acceptable salt or prodrug thereof in connection with the present invention include, but are not limited to, the compounds set forth in Table 4B below:

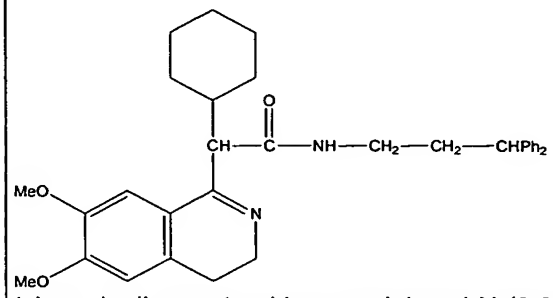
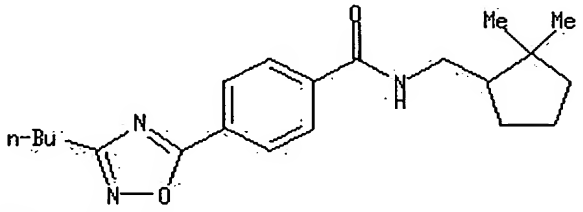
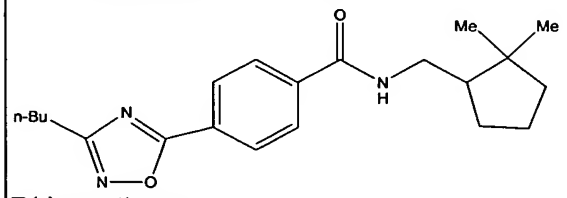
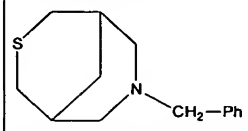
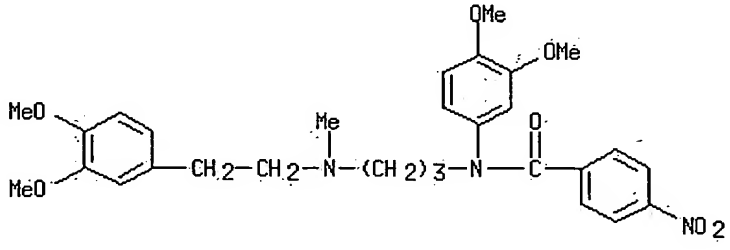
TABLE 4B

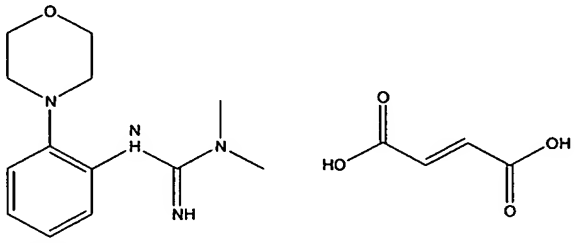
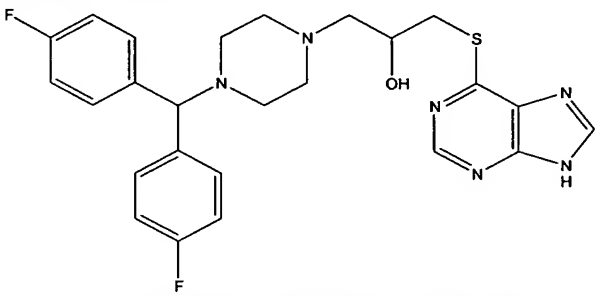
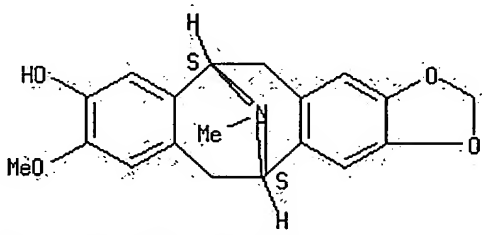
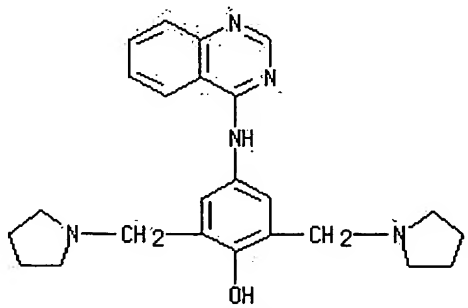
EXAMPLES OF POTASSIUM ION CHANNEL BLOCKERS AS EMBODIMENTS

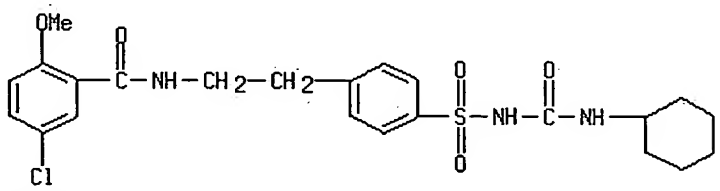
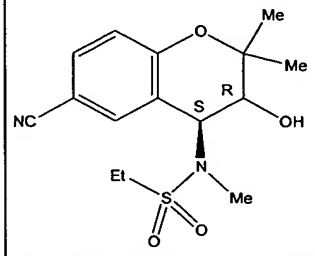
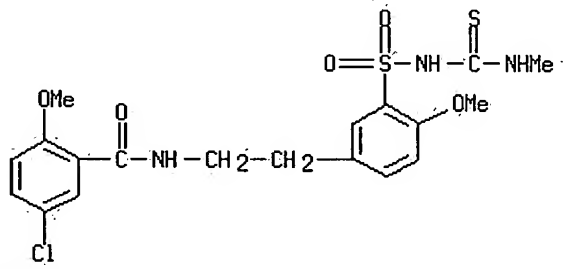
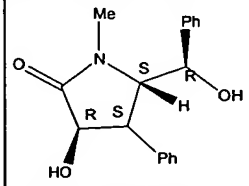
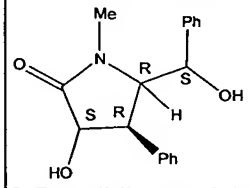
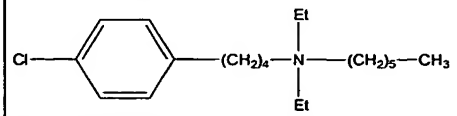
ID	Common Name	Structure Chemical Name	CAS Registry Number
1	Acecainide	 Benzamide, 4-(acetylamino)-N-[2-(diethylamino)ethyl]-	32795-44-1
2	AL 275	No name available. No structure available.	331677-71-5
3	Alinidine ST 567	 1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)-4,5-dihydro-N-2-propenyl-	33178-86-8
4	N-allyl secoboldine	 2,6-Phenanthrenediol, 3,5-dimethoxy-8-[2-(methyl-2-propenylamino)ethyl]-	157200-09-4

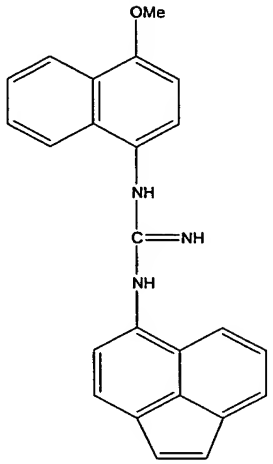
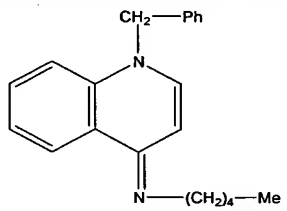
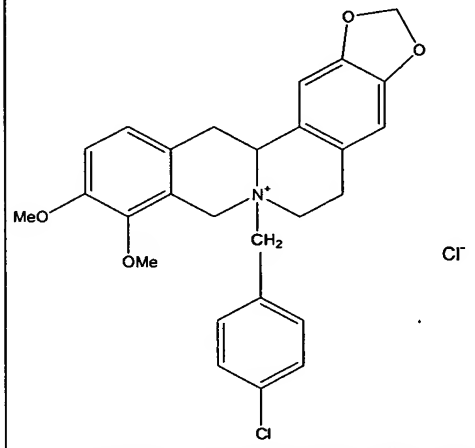
ID	Common Name	Structure Chemical Name	CAS Registry Number
5	Almokalant H 234/09	 Benzonitrile, 4-[3-[ethyl[3-(propylsulfinyl)propyl]amino]-2-hydroxypropoxy]-	123955-10-2
6	AM 92016	 Methanesulfonamide, N-[4-[3-[[2-(3,4-dichlorophenyl)ethyl]methylamino]-2-hydroxypropoxy]phenyl]-, monobenzoate (salt)	178894-81-0
7	Ambasilide LU 47110	 3,7-Diazabicyclo[3.3.1]nonane, 3-(4-aminobenzoyl)-7-(phenylmethyl)-	83991-25-7
8	AN 132	 Propanamide, 3-[[2-[bis(1-methylethyl)amino]ethyl]amino]-N-(2,6-dimethylphenyl)-,phosphate(1:2)	105668-70-0
9	ARH 050642	No name available. No structure available	No CAS RN
10	AWD 12-260	 [3,4'-Bipyridine]-5-carbonitrile, 6-[[3-(diethylamino)propyl]amino]-	108610-89-5
11	AWD 23-111 AWD 160275 (oxalate salt)	 Benzamide, N-[2-(dicyclohexylamino)-2-oxoethyl]-N-[3-(diethylamino)propyl]-4-nitro-, monohydrochloride	221639-91-4 (HCl) 226408-59-9 (oxalate)
12	AZD 7009	No name available. No structure available	No CAS RN

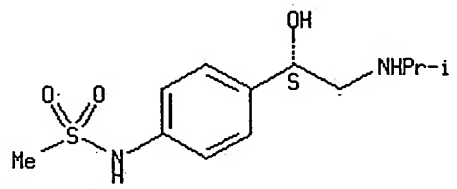
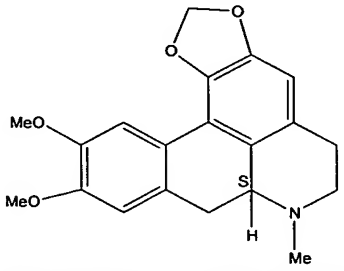
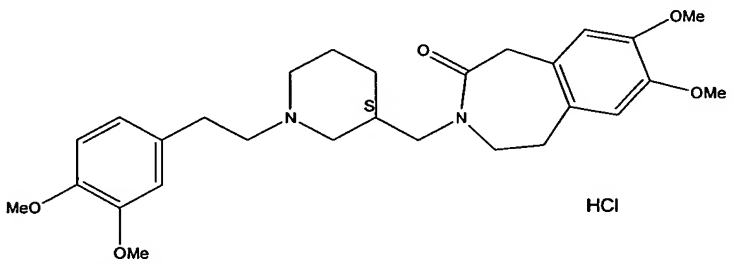
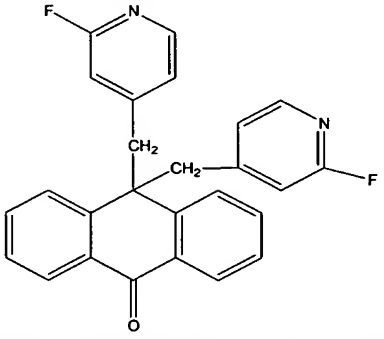
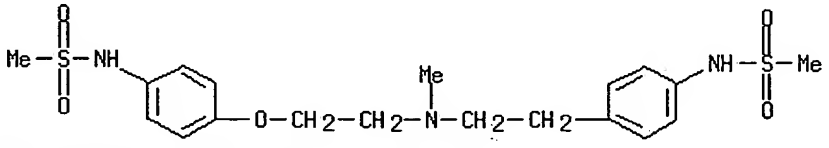
ID	Common Name	Structure Chemical Name	CAS Registry Number
13	AZDF 265	 Benzoic acid, 4-[2-oxo-2-[[phenyl[2-(1-piperidinyl)phenyl]methyl]amino]ethyl]-	83901-40-0
14	Azimilide	 2,4-Imidazolidinedione, 1-[[[5-(4-chlorophenyl)-2-furanyl]methylene]amino]-3-[4-(4-methyl-1-piperazinyl)butyl]-, dihydrochloride	149888-94-8
15	Bepridil	 1-Pyrrolidineethanamine, β-[(2-methylpropoxy) methyl]-N-phenyl-N-(phenylmethyl)-	64706-54-3
16	Bertosamil	 Spiro[cyclohexane-1,9'-[3,7]diazabicyclo[3.3.1]nonane],3'-(1-methylethyl)-7'-(2-methylpropyl)-	126825-36-3

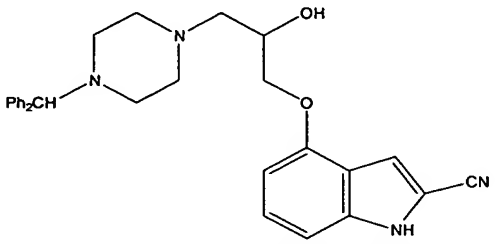
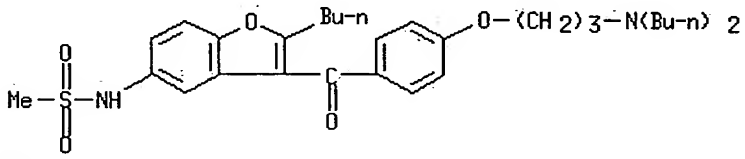
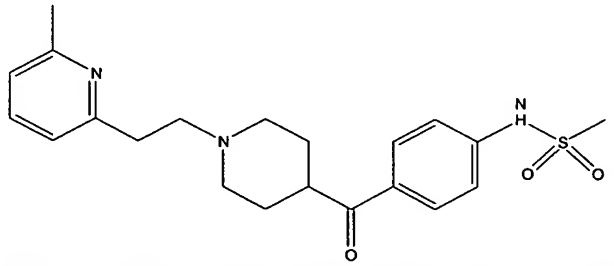
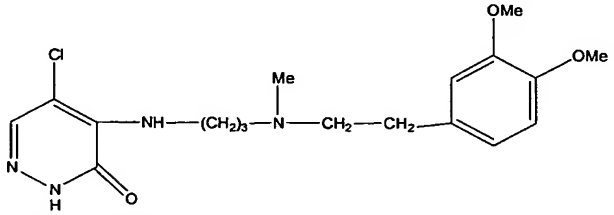
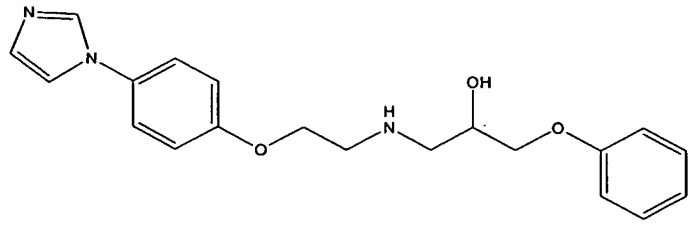
ID	Common Name	Structure Chemical Name	CAS Registry Number
17	BIIA 0388	 1-Isoquinolineacetamide, α-cyclohexyl-N-(3,3-diphenylpropyl)-3,4-dihydro-6,7-dimethoxy-	337359-07-6
18	BMS 208782	 S(+)enantiomer Benzamide, 4-(3-butyl-1,2,4-oxadiazol-5-yl)-N-[(2,2-dimethylcyclopentyl)methyl]-, (+)-	212380-81-9
19	BMS 208783	 R(-)enantiomer Benzamide, 4-(3-butyl-1,2,4-oxadiazol-5-yl)-N-[(2,2-dimethylcyclopentyl)methyl]-, (-)-	212380-82-0
20	BRBI 28	 3-Thia-7-azabicyclo[3.3.1]nonane, 7-(phenylmethyl)-, perchlorate	89398-07-2
21	BRL 32872	 # HCl Benzamide, N-(3,4-dimethoxyphenyl)-N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-4-nitro-, monohydrochloride	113241-47-7

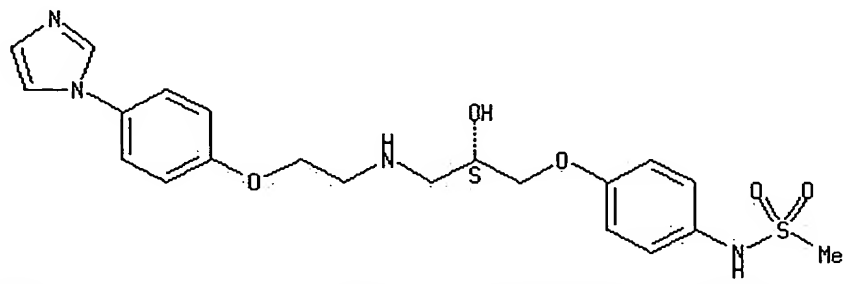
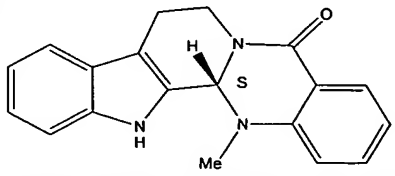
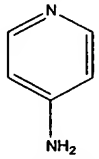
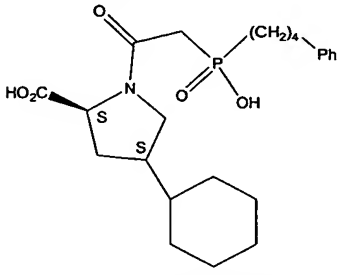
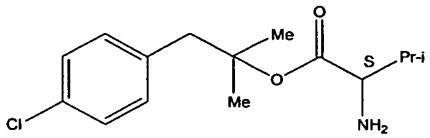
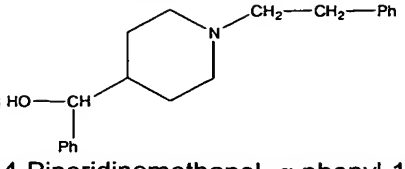
ID	Common Name	Structure Chemical Name	CAS Registry Number
22	BTS 67582	 Guanidine, N,N-dimethyl-N'-[2-(4-morpholinyl)phenyl]-, (2E)-2-butenedioate (1:1)	161748-40-9
23	Carsatrin Succiniate RWJ 24517	 1-Piperazineethanol, 4-[bis(4-fluorophenyl)methyl]-α-[(1H-purin-6-ylthio)methyl]-	125363-87-3 132199-13-4 Succinate
24	Caryachine	 Benzo[5,6]cycloocta[1,2-f]-1,3-benzodioxol-5,11-imin-9-ol, 5,6,11,12-tetrahydro-8-methoxy-14-methyl-, (5S,11S)-	37687-27-7
25	CGX 1007	Conotoxin GV L-Aspartamide, glycyl-L-α-glutamyl-4-carboxy-L-α-glutamyl-4-carboxy-L-α-glutamyl-L-leucyl-L-glutaminyl-4-carboxy-L-α-glutamyl-L-asparaginyl-L-glutaminyl-4-carboxy-L-α-glutamyl-L-leucyl- L-isoleucyl-L-arginyl-4-carboxy-L-α-glutamyl-L-lysyl-L-seryl-	93438-65-4
26	Changrolin Pyrozoline	 Phenol, 2,6-bis(1-pyrrolidinylmethyl)-4-(4-quinazolinylamino)-	72063-47-9

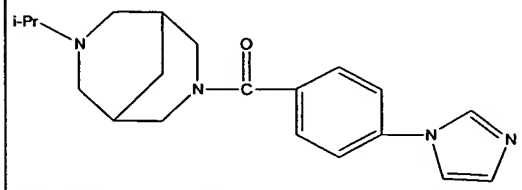
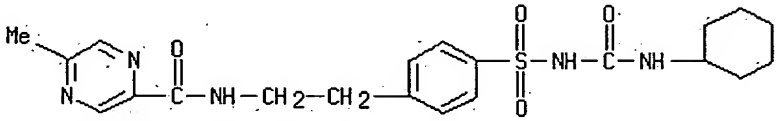
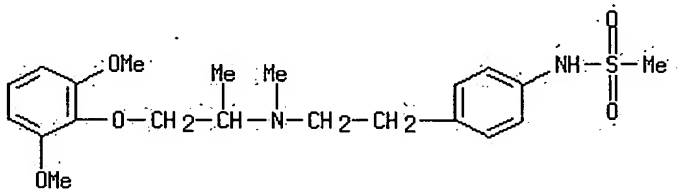
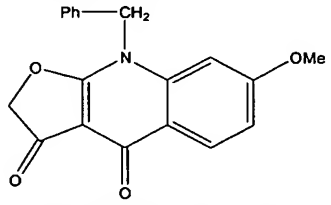
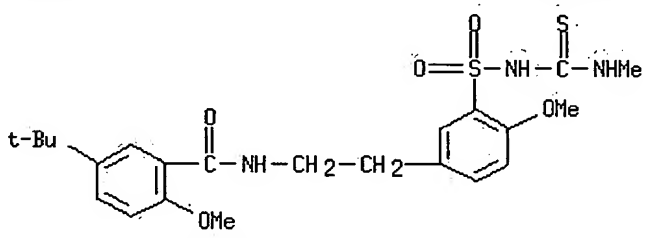
ID	Common Name	Structure Chemical Name	CAS Registry Number
27	CHF 1522 Cyclo-dextrin complex of glibenclamide	 Benzamide, 5-chloro-N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-2-methoxy-	10238-21-8
28	Chromanol 293 isomer	 Ethanesulfonamide, N-[(3R,4S)-6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl]-2H-1-benzopyran-4-yl]-N-methyl-, rel-	163163-23-3
29	Clamikalant HMR 1883 HMR 1098 (Na salt)	 Benzamide, 5-chloro-2-methoxy-N-[2-[4-methoxy-3-[[[(methylamino)thioxomethyl]amino]sulfonyl]phenyl]ethyl]-	158751-64-5
30	Clausenami de (racemic)	 2-Pyrrolidinone, 3-hydroxy-5-[(R)-hydroxyphenylmethyl]-1-methyl-4-phenyl-,(3R,4S,5S)-rel-	103541-15-7
31	(-) clausenami de	 2-Pyrrolidinone, 3-hydroxy-5-[(S)-hydroxyphenylmethyl]-1-methyl-4-phenyl-, (3S,4R,5R)-	201529-58-0
32	Clofilium LY 150378	 Benzenebutanaminium, 4-chloro-N,N-diethyl-N-heptyl	68379-02-2

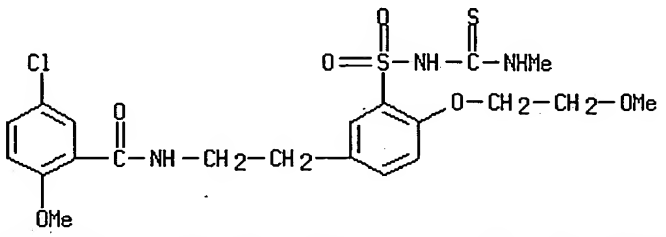
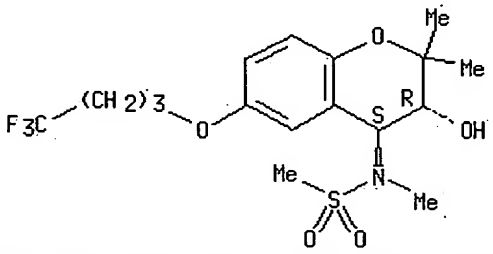
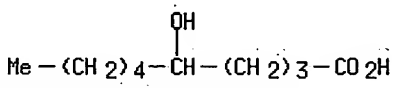
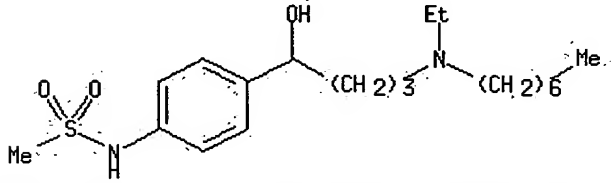
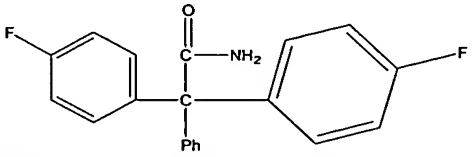
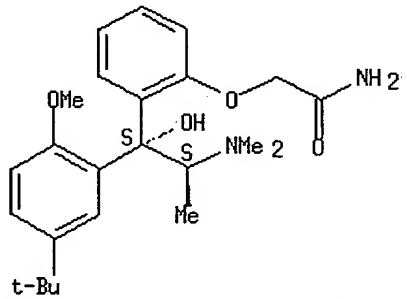
ID	Common Name	Structure Chemical Name	CAS Registry Number
33	CNS 1237	 Guanidine, N-5-acenaphthylenyl-N'-(4-methoxy-1-naphthalenyl)-	174232-22-5
34	CP 92713	No name available. No structure available	No CAS RN
35	CP 308408	No name available. No structure available	No CAS RN
36	CP 339818	 1-Pentanamine, N-[1-(phenylmethyl)-4(1H)-quinolinylidene]-	185855-91-8
37	CP 366660	No name available. No structure available	No CAS RN
38	CPU 86017	 6H-Benzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium, 7-[(4-chlorophenyl)methyl]-5,8,13,13a-tetrahydro-9,10-dimethoxy-,choloride	149088-32-4

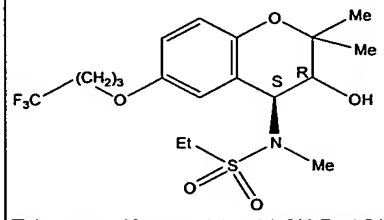
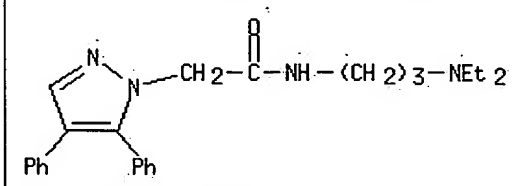
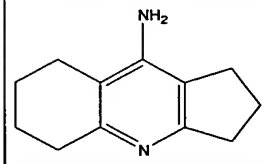
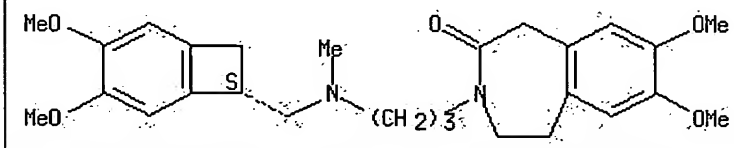
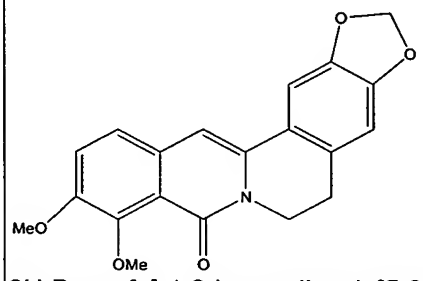
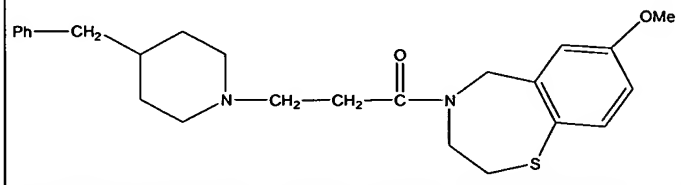
ID	Common Name	Structure Chemical Name	CAS Registry Number
39	Dexsotalol BMY 057631D d-sotalol	 Methanesulfonamide, N-[4-[(1S)-1-hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]-	30236-32-9
40	Dicentrine	 5H-Benzo[g]-1,3-benzodioxolo[6,5,4-de]quinoline, 6,7,7a,8-tetrahydro-10,11-dimethoxy-7-methyl-,(7aS)-	517-66-8
41	DK AH 269	 2H-3-Benzazepin-2-one,3-[[(3S)-1-[2-(3,4-dimethoxyphenyl)ethyl]-3-piperidinyl]methyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-,monohydrochloride	186097-54-1
42	DMP 543 DPC 543	 9(10H)-Anthracenone,10,10-bis[(2-fluoro-4-pyridinyl)methyl]-	160588-45-4
43	Dofetilide	 Methanesulfonamide, N-[4-[2-[methyl[2-[4-[(methylsulfonyl)amino]phenoxy]ethyl]amino]ethyl]phenyl]-	115256-11-6

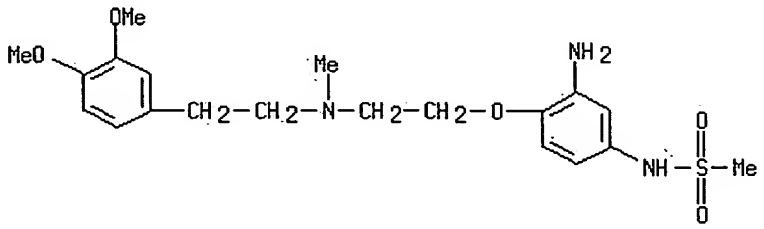
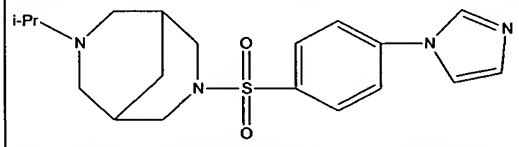
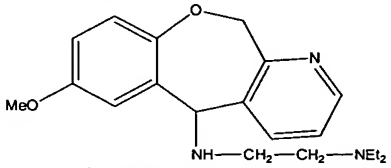
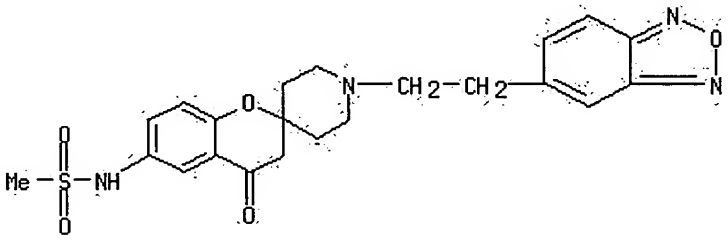
ID	Common Name	Structure Chemical Name	CAS Registry Number
44	DPI 201106	 1H-Indole-2-carbonitrile,4-[3-[4-(diphenylmethyl)-1-piperazinyl]-2-hydroxypropoxy]-	78573-03-2
45	Dronedarone SR 33589	 Methanesulfonamide, N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]-	141626-36-0
46	E 4031	 Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-,dihydrochloride	113559-13-0
47	EGIS 7229 S 21407	 3(2H)-Pyridazinone,5-chloro-4-[[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]amino]-,(2E)-2-butenedioate (1:1)	190333-92-7
48	(+/-) Ersentilide	 Methanesulfonamide, N-[4-[2-hydroxy-3-[[2-[4-(1H-imidazol-1-yl)phenoxy]ethyl]amino]propoxy]phenyl]-	128264-20-0

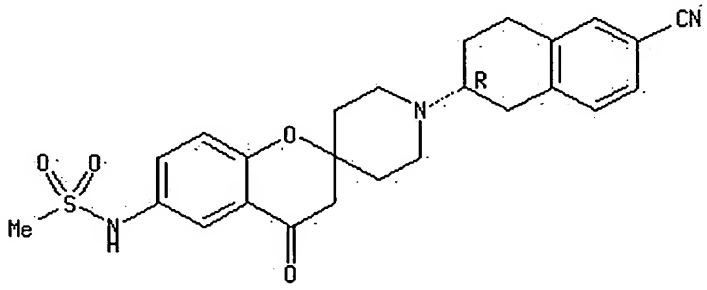
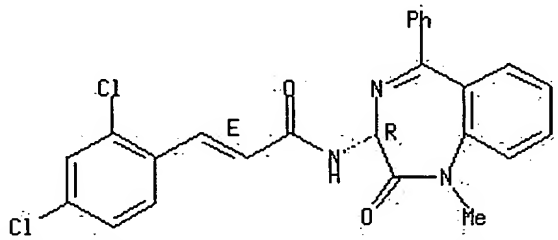
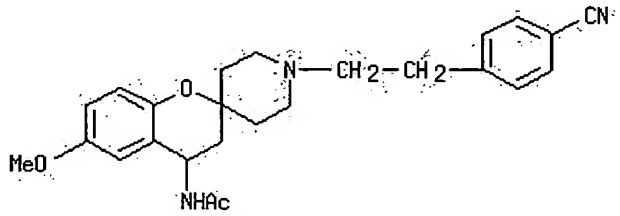
ID	Common Name	Structure Chemical Name	CAS Registry Number
49	(S)-ersentilide	 Methanesulfonamide, N-[4-[(2S)-2-hydroxy-3-[[2-[4-(1H-imidazol-1-yl)phenoxy]ethyl]amino]propoxy]phenyl]-	125279-79-0
50	Evodiamine (S)	 Indolo[2',3',3,4]pyrido[2,1-b]quinazolin-5(7H)-one, 8,13,13b,14-tetrahydro-14-methyl-, (13bS)-	518-17-2
51	Fampridine 4-aminopyridine EL 970	 4-Pyridinamine	504-24-5
52	Fosinoprilat	 L-Proline, 4-cyclohexyl-l-[[hydroxy(4-phenylbutyl)phosphinyl]acetyl]-, (4S)-	95399-71-6
53	GEA 857	 L-Valine, 2-(4-chlorophenyl)-1,1-dimethylethyl ester	120493-42-7
54	Glemanserin MDL 11939	 4-Piperidinemethanol, α-phenyl-1-(2-phenylethyl)-	107703-78-6

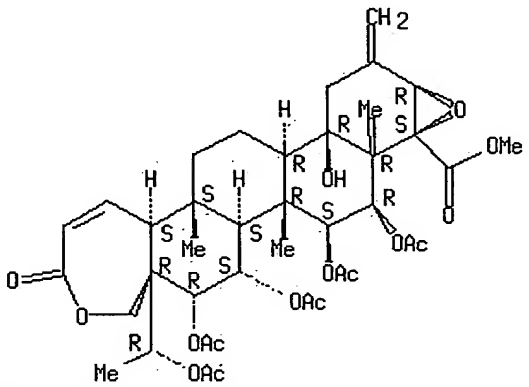
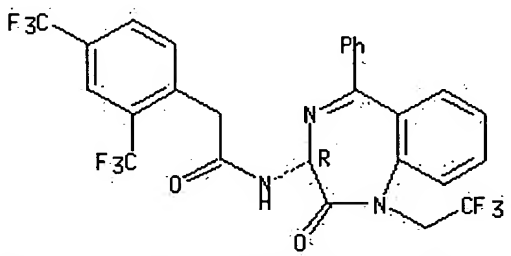
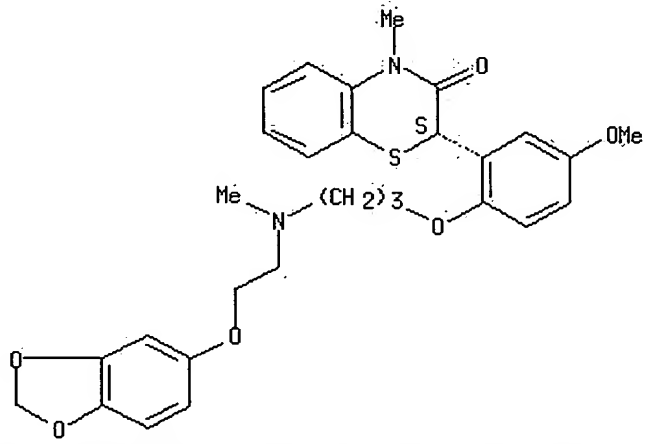
ID	Common Name	Structure Chemical Name	CAS Registry Number
55	GLG V 13	 3,7-Diazabicyclo[3.3.1]nanone, 3-[4-(1H-imidazol-1-yl)benzoyl]-7-(1-methylethyl)-, diperchlorate	155029-33-7
56	Glipizide K 4024 TK 1320	 Pyrazinecarboxamide, N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methyl-	29094-61-9
57	GYKI 16638	 Methanesulfonamide, N-[4-[2-[[2-(2,6-dimethoxyphenoxy)-1-methylethyl]methylamino]ethyl]phenyl]-, monohydrochloride	307556-59-8
58	HA 7	 Furo[2,3-b]quinoline-3,4(2H,9H)-dione, 7-methoxy-9-(phenylmethyl)-	201943-88-6
59	HMR 1372	 Benzamide, 5-(1,1-dimethylethyl)-2-methoxy-N-[2-[4-methoxy-3-[[[(methylamino)thioxomethyl]amino]sulfonyl]phenyl]ethyl]-	260971-17-3

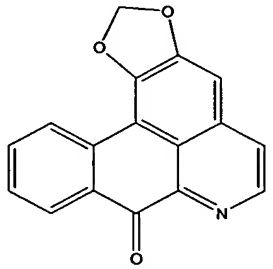
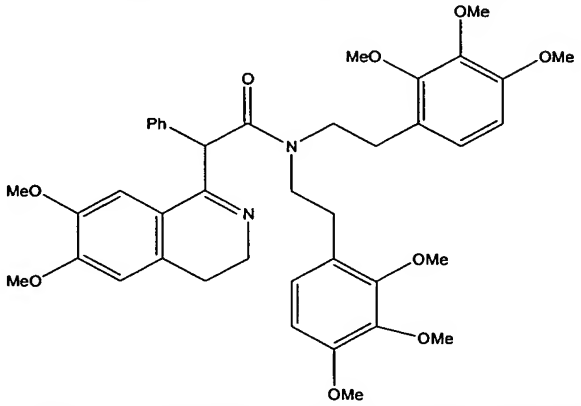
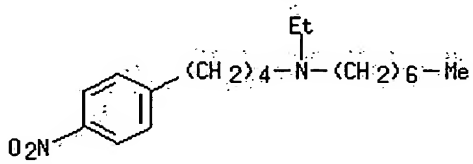
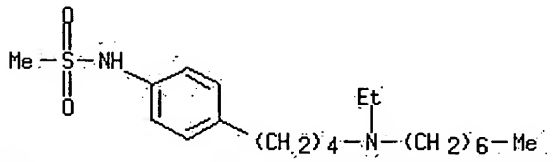
ID	Common Name	Structure Chemical Name	CAS Registry Number
60	HMR 1402	 Benzamide, 5-chloro-2-methoxy-N-[2-[4-(2-methoxyethoxy)-3-[[[(methylamino)thioxomethyl]amino]sulfonyl]phenyl]ethyl]-	181272-10-6
61	HMR 1556	 Methanesulfonamide, N-[(3R,4S)-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)-2H-1-benzopyran-4-yl]-N-methyl-	223749-46-0
62	Hydroxy decanoate	 Decanoic acid, 5-hydroxy-	624-00-0
63	Ibutilide U 70226E (solatol analog)	 Methanesulfonamide, N-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl]-	122647-31-8
64	ICA 17043	 Benzeneacetamide, 4-fluoro-α-(4-fluorophenyl)-α-phenyl-	289656-45-7
65	ICI 181037	 Acetamide, 2-[2-[2-(dimethylamino)-1-[5-(1,1-dimethylethyl)-2-methoxyphenyl]-1-hydroxypropyl]phenoxy]-, (R*,R*)-	138779-29-0

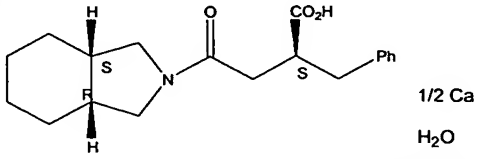
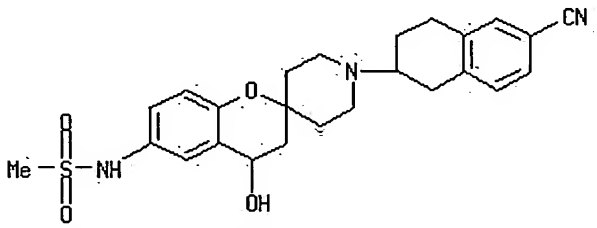
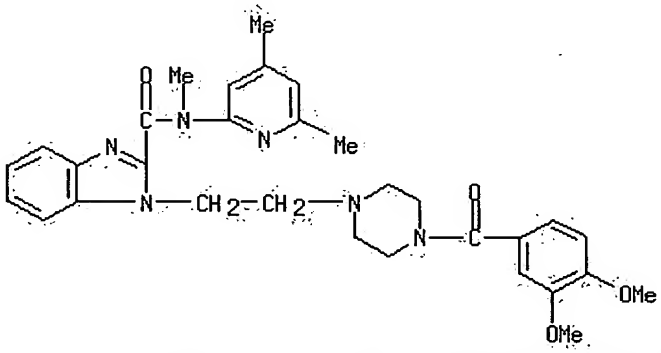
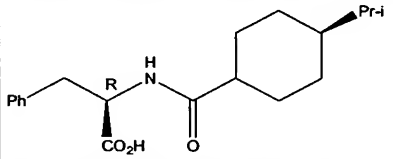
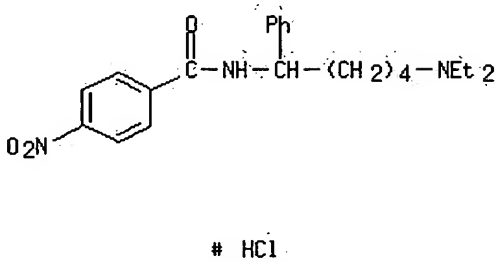
ID	Common Name	Structure Chemical Name	CAS Registry Number
66	IK Channel Blocker	 Ethanesulfonamide, N-[(3R,4S)-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)-2H-1-benzopyran-4-yl]-N-methyl-	223749-45-9
67	Ipazilide WIN 54177	 1H-Pyrazole-1-acetamide, N-[3-(diethylamino)propyl]-4,5-diphenyl-	115436-73-2
68	Ipidacrine NIK 247	 1H-Cyclopenta[b]quinolin-9-amine, 2,3,5,6,7,8-hexahydro-	62732-44-9
69	Ivabradine	 2H-3-Benzazepin-2-one, 3-[3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-	155974-00-8
70	JKL 1073A Oxy-berberine; 8-Oxo-berberine; 8-Oxy-berberine; Berlambine	 8H-Benzo[g]-1,3-benzodioxolo[5,6-a]quinolizin-8-one, 5,6-dihydro-9,10-dimethoxy-	549-21-3
71	JTV 519	 1,4-Benzothiazepine, 2,3,4,5-tetrahydro-7-methoxy-4-[1-oxo-3-[4-(phenylmethyl)-1-piperidinyl]propyl]	145903-06-6

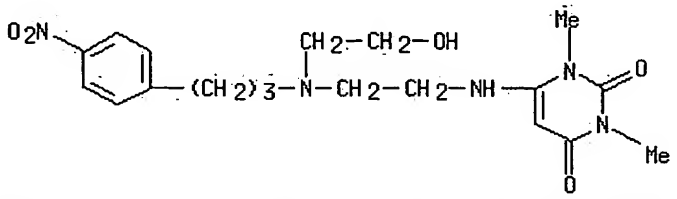
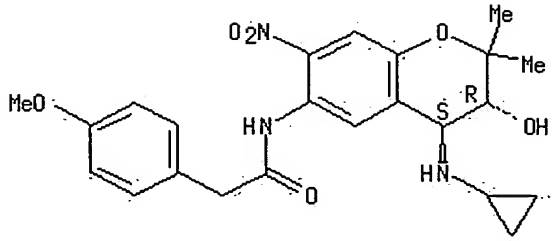
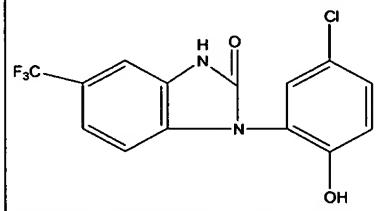
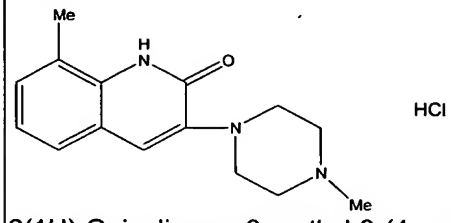
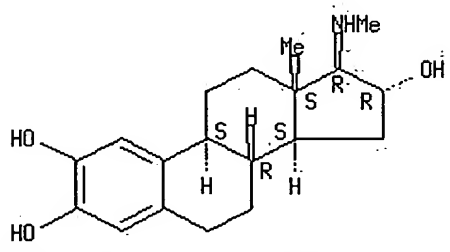
ID	Common Name	Structure Chemical Name	CAS Registry Number
72	KCB 328	 # HCl Methanesulfonamide, N-[3-amino-4-[2-[[2-(3,4-dimethoxyphenyl) ethyl]methylamino]ethoxy]phenyl]-,monohydrochloride	177596-55-3
73	KMC IV 84	 3,7-Diazabicyclo[3.3.1]nonane, 3-[[4-(1H-imidazol-1-yl)phenyl]sulfonyl]-7-(1-methylethyl)-, diperchlorate	190315-04-9
74	KW 3407	 1,2-Ethanediamine, N'-(5,11-dihydro-7-methoxy[1]benzoxepino[3,4-b]pyridin-5-yl)-N,N-diethyl-, (2E)-2-butenedioate (2:3)	115750-37-3
75	L 691121	 # HCl Methanesulfonamide, N-[1'-[2-(2,1,3-benzoxadiazol-5-yl)ethyl]-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, monohydrochloride	136075-60-0

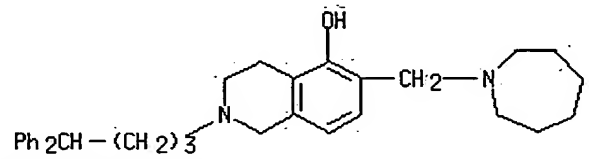
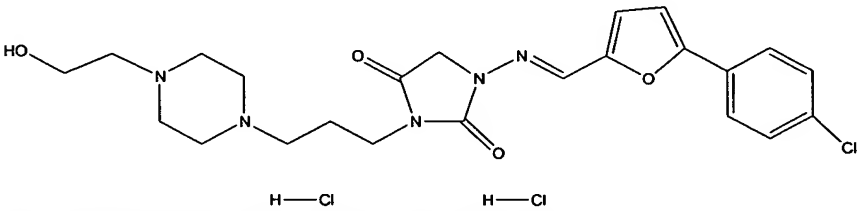
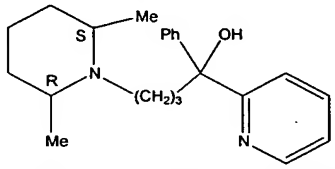
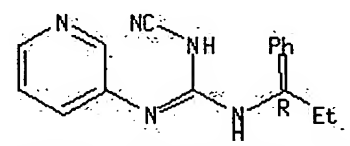
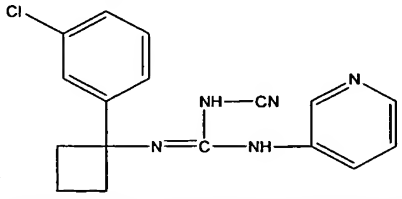
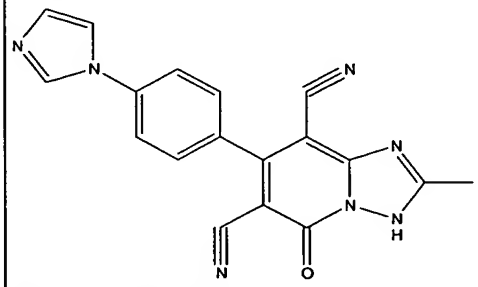
ID	Common Name	Structure Chemical Name	CAS Registry Number
76	L 702958	 # HCl Methanesulfonamide, N-[1'-[(2R)-6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl]-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, monohydrochloride	136078-58-5
77	L 735821	 2-Propenamide, 3-(2,4-dichlorophenyl)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-, (2E)-	170228-29-2
78	L 742084	 Acetamide, N-[1'-[2-(4-cyanophenyl)ethyl]-3,4-dihydro-6-methoxyspiro[2H-1-benzopyran-2,4'-piperidin]-4-yl]-	171797-60-7 171797-59-4 (HCl)

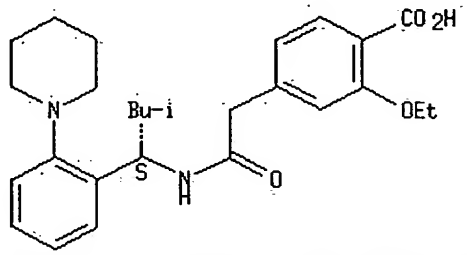
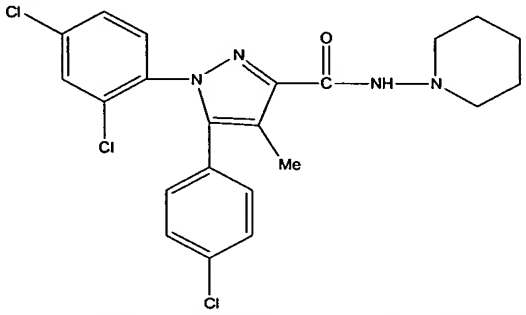
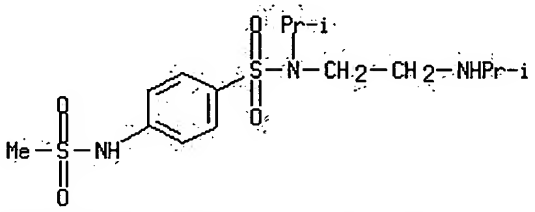
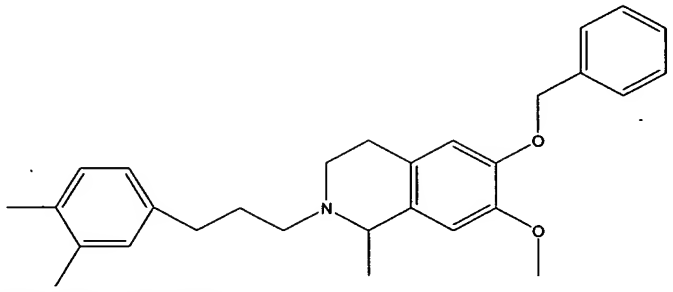
ID	Common Name	Structure Chemical Name	CAS Registry Number
79	L755860	 Oxireno[7,8]chryseno[2,1-c]oxepin-1a(1bH)-carboxylic acid,2,3,4,5-tetrakis(acetyloxy)-5a-[(1R)-1-(acetyloxy)ethyl]-2,3,3a,3b,4,5,5a,6,8,10a,10b,11,12,12a,12b,13,14,14a-octadecahydro-12b-hydroxy-1b,3a,10b-trimethyl-14-methylene-8-oxo-, methyl ester,(1aS,1bR,2R,3S,3aR,3bS,4S,5R,5aR,10aS,10bS,12aR,12bR,14aR)- Correolide	190017-00-6 and related compounds
80	L 768673	 Benzeneacetamide, N-[(3R)-2,3-dihydro-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepin-3-yl]-2,4-bis(trifluoromethyl)-	177954-68-6
81	Levosemotiadil SA 3212 SD 3212	 2H-1,4-Benzothiazin-3(4H)-one, 2-[2-[3-[[2-(1,3-benzodioxol-5-yloxy)ethyl]methylamino]propoxy]-5-methoxyphenyl]-4-methyl-, (2S)-, (2E)-2-butenedioate (1:1)	116476-17-6 (1:1 salt) 116476-16-5

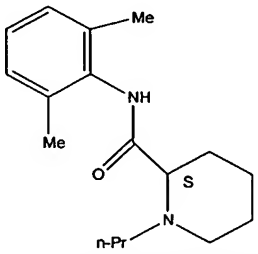
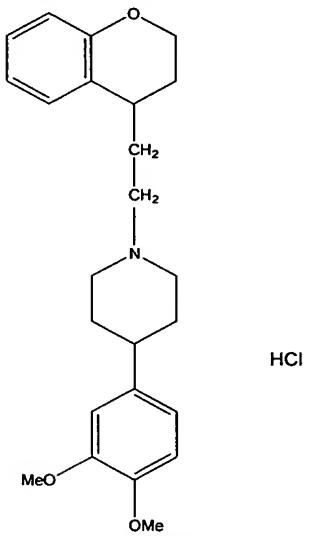
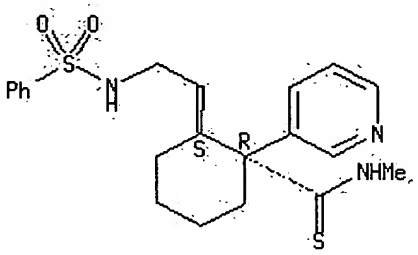
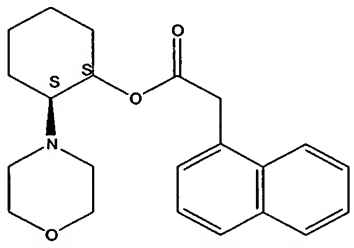
ID	Common Name	Structure Chemical Name	CAS Registry Number
82	Liriodenine	 8H-Benzo[g]-1,3-benzodioxolo[6,5,4-de]quinolin-8-one	475-75-2
83	LOE 908 Pinokalant	 1-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-α-phenyl-N,N-bis[2-(2,3,4-trimethoxyphenyl)ethyl]-	149759-26-2
84	LY 97241	 Benzenebutanamine, N-ethyl-N-heptyl-4-nitro-	72456-63-4
85	LY 190147	 Methanesulfonamide, N-[4-[4-(ethylheptylamino)butyl]phenyl]-	100632-59-5
86	Margatoxin	Structure Diagram not available L-Histidine, L-threonyl-L-isoleucyl-L-isoleucyl-L-asparaginyl-L-valyl-L-lysyl-L-cysteinyl-L-threonyl-L-seryl-L-prolyl-L-lysyl-L-glutaminyl-L-cysteinyl-L-leucyl-L-prolyl-L-prolyl-L-cysteinyl-L-lysyl-L-alanyl-L-glutaminyl-L-phenylalanylglycyl-L-glutaminyl-L-seryl-L-alanylglycyl-L-alanyl-L-lysyl-L-cysteinyl-L-methionyl-L-asparaginylglycyl-L-lysyl-L-cysteinyl-L-lysyl-L-cysteinyl-L-tyrosyl-L-prolyl-, cyclic (7→29),(13→34),(17→36)-tris(disulfide)	145808-47-5

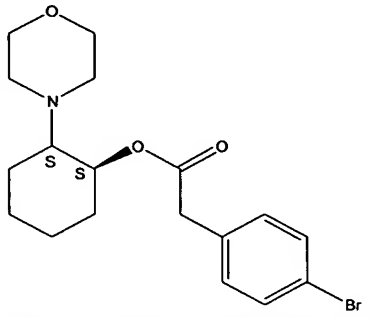
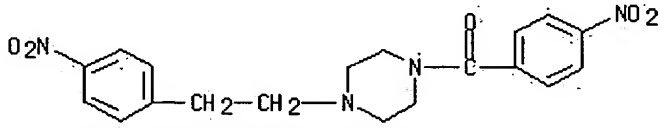
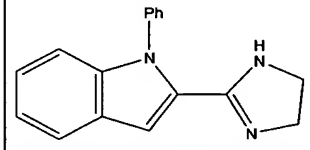
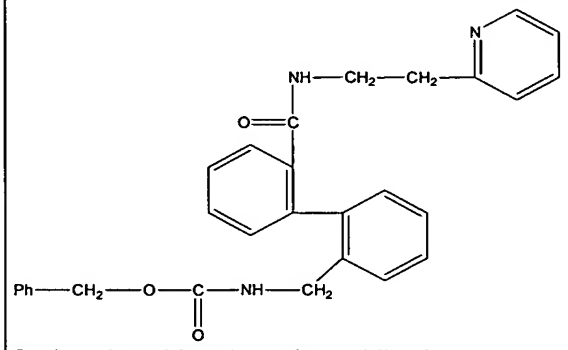
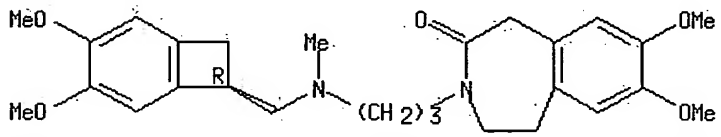
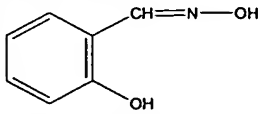
ID	Common Name	Structure Chemical Name	CAS Registry Number
87	Mitiglinide KAD 1229 S-21403	 1/2 Ca H_2O 2H-Isoindole-2-butanoic acid, octahydro-γ-oxo-α-(phenylmethyl)-, calcium salt, dihydrate, (αS,3aR,7aS)-	207844-01-7
88	MK 499 L 706000	 Methanesulfonamide, N-[(4R)-1'-[(2R)-6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl]-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, rel-	150481-98-4
89	N 3601	 1H-Benzimidazole-2-carboxamide, 1-[2-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]ethyl]-N-(4,6-dimethyl-2-pyridinyl)-N-methyl- (9CI)	113826-99-6 (maleate salt)
90	Nateglinide AY 4166 YM 026 SDZ DNJ 608	 D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-	105816-04-4
91	Nibentan	 # HCl Benzamide, N-[5-(diethylamino)-1-phenylpentyl]-4-nitro-, monohydrochloride	157832-56-9

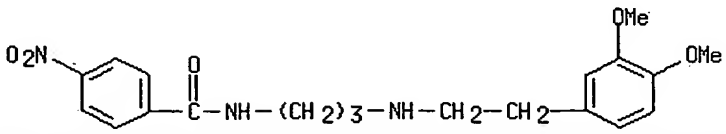
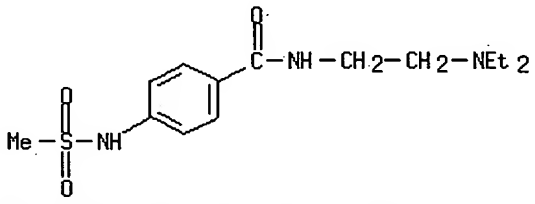
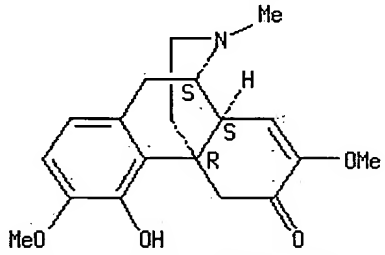
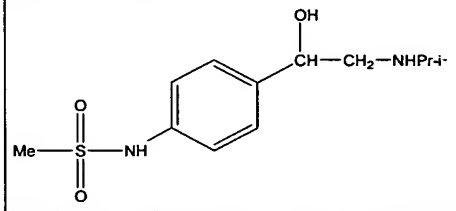
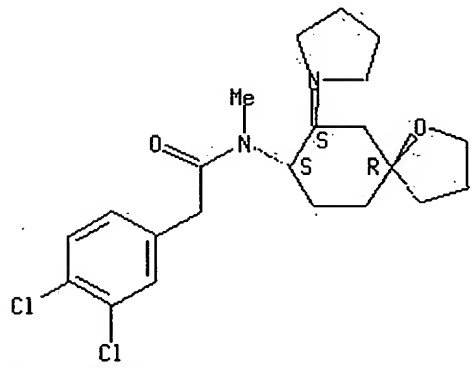
ID	Common Name	Structure Chemical Name	CAS Registry Number
92	Nifekalant MS 551 (HCl)	 2,4(1H,3H)-Pyrimidinedione, 6-[[2-[(2-hydroxyethyl)[3-(4-nitrophenyl)propyl]amino]ethyl]amino]-1,3-dimethyl-	130636-43-0 130656-51-8 (HCl)
93	NIP 142	 Benzeneacetamide, N-[4-(cyclopropylamino)-3,4-dihydro-3-hydroxy-2,2-dimethyl-7-nitro-2H-1-benzopyran-6-yl]-4-methoxy-, (3R-trans)-	344609-47-8 (no structure) 203002-75-9
94	NS 004	 2H-Benzimidazol-2-one, 1-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-5-(trifluoromethyl)-	141797-92-4
95	NS 1546	No name available. No structure available	No CAS RN
96	OPC 88117	 2(1H)-Quinolinone, 8-methyl-3-(4-methyl-1-piperazinyl)-, monohydrochloride	113225-73-3
97	ORG 20781	 Estra-1,3,5(10)-triene-2,3,16-triol, 17-(methylamino)-, (16α,17β)-	169107-07-7

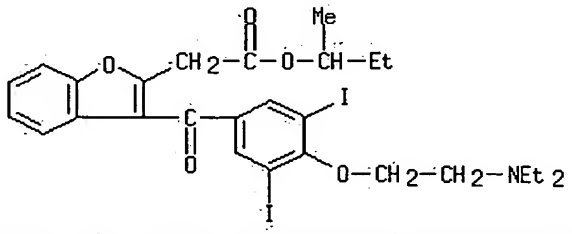
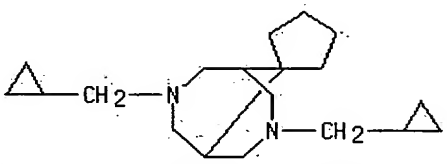
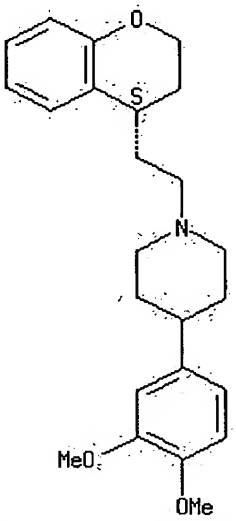
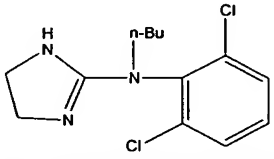
ID	Common Name	Structure Chemical Name	CAS Registry Number
98	PD 157667	 5-Isoquinolinol, 2-(4,4-diphenylbutyl-6-[(hexahydro-1H-azepin-1-yl)methyl]-1,2,3,4-tetrahyro-	208925-23-9
99	PGE 844384	 2,4-Imidazolidinedione,1-[[[5-(4-chlorophenyl)-2-furanyl]methylene]amino]-3-[3-[4-(2-hydroxyethyl)-1-piperazinyl]propyl]-,dihydrochloride	149889-02-1
100	Pirmenol CI 845	 2-Pyridinemethanol, α-[3-[(2R,6S)-2,6-dimethyl-1-piperidinyl]propyl]-α-phenyl-, rel-	68252-19-7
101	PNU 96293	 Guanidine, N-cyano-N'-(1-phenylpropyl)-N''-3-pyridinyl-, (R)-	155342-80-6
102	PNU 99963	 Guanidine, N-[1-(3-chlorophenyl)cyclobutyl]-N'-cyano-N''-3-pyridinyl-	158942-98-4
103	Pyrido triazoles	 No name available	No CAS RN

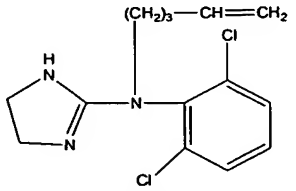
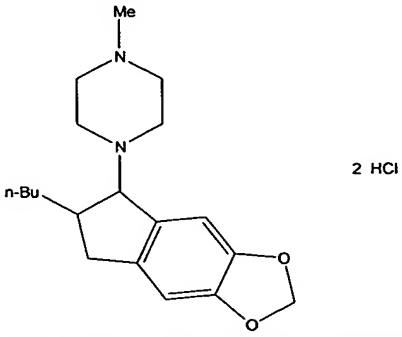
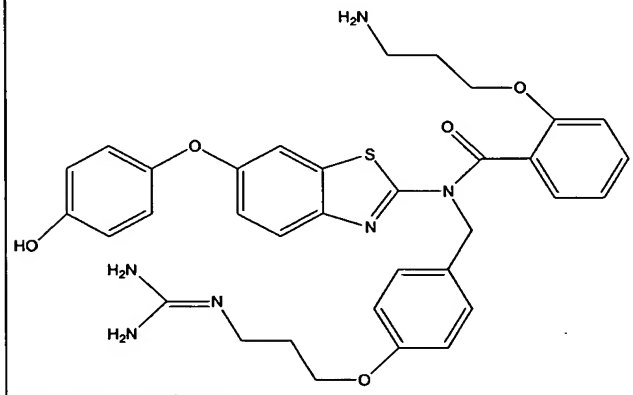
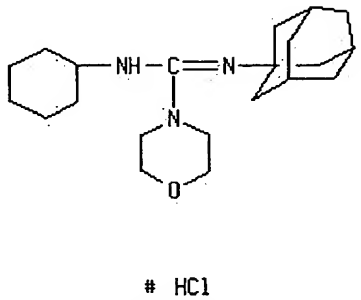
ID	Common Name	Structure Chemical Name	CAS Registry Number
104	Repaglinide NN 623 AGEE 623	 Benzoic acid, 2-ethoxy-4-[2-[[(1S)-3-methyl-1-[2-(1-piperidinyl)phenyl] butyl]amino]-2-oxoethyl]-	135062-02-1
105	Rimonabant SR 141716	 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-	168273-06-1
106	Risotilide	 Benzenesulfonamide, N-(1-methylethyl)-N-[2-[(1-methylethyl)amino]ethyl]-4-[(methylsulfonyl)amino]-	120688-08-6
107	Ro-034563	 No name available	No CAS RN

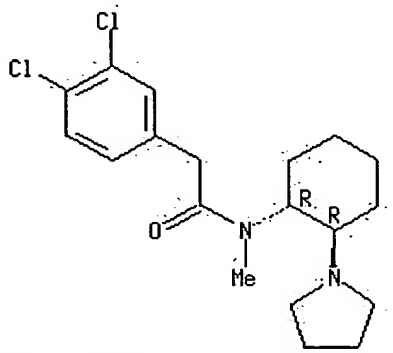
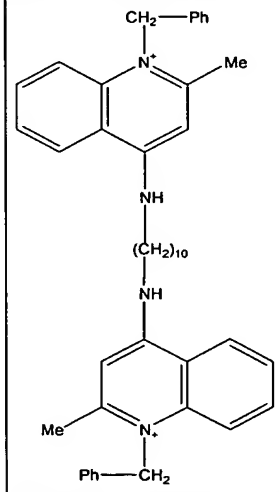
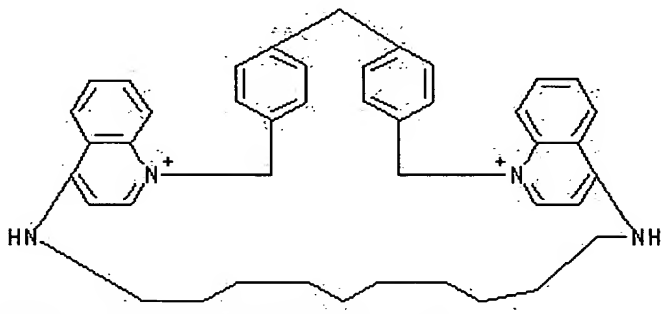
ID	Common Name	Structure Chemical Name	CAS Registry Number
108	Ropivacaine AL 281 LEA 103	 2-Piperidinecarboxamide, N-(2,6-dimethylphenyl)-1-propyl-, (2S)-	84057-95-4
109	RP 58866	 Piperidine, 1-[2-(3,4-dihydro-2H-1-benzopyran-4-yl)ethyl]-4-(3,4-dimethoxyphenyl)-, hydrochloride	121277-95-0
110	RP 66784	 Cyclohexanecarbothioamide, N-methyl-2-[2-[(phenylsulfonyl)amino]ethyl]-1-(3-pyridinyl)-, trans-	137392-34-8
111	RSD 1000	 1-Naphthaleneacetic acid, (1R,2R)-2-(4-morpholinyl)cyclohexyl ester, rel-	169191-56-4

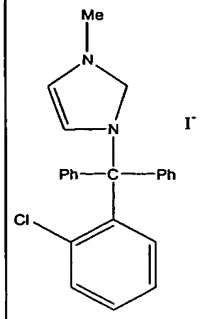
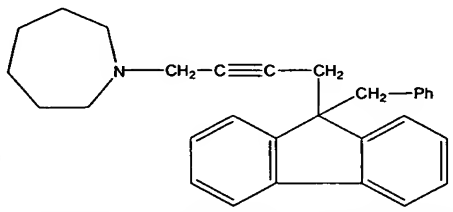
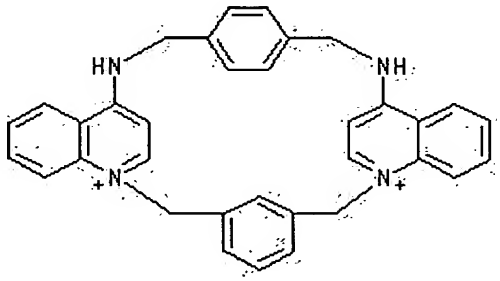
ID	Common Name	Structure Chemical Name	CAS Registry Number
112	RSD 1019	 Benzeneacetic acid, 4-bromo-, (1R,2R)-2-(4-morpholinyl)cyclohexyl ester, rel-	169191-65-5
113	RWJ 28810	 Piperazine, 1-(4-nitrobenzoyl-4-[2-(4-nitrophenyl)ethyl]-	329040-80-4
114	RX 871024	 1H-Indole, 2-(4,5-dihydro-1H-imidazol-2-yl)-1-phenyl-	142872-83-1
115	S 9947	 Carbamic acid, [[2'-[[[2-(2-pyridinyl)ethyl]amino]carbonyl][1,1'-biphenyl]-2-yl]methyl]-, phenylmethyl ester	332378-43-5
116	S 16260	 2H-3-Benzazepin-2-one, 3-[3-[[[(7R)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-	167072-91-5
117	Salicylaldoxime	 Benzaldehyde, 2-hydroxy-, oxime	94-67-7

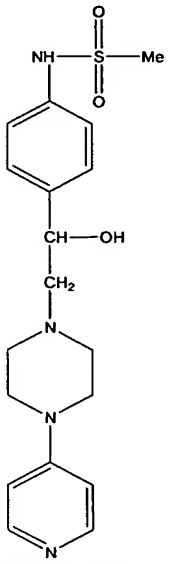
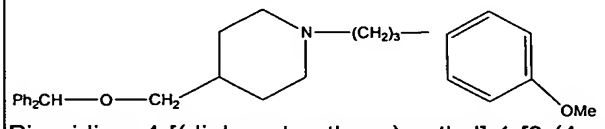
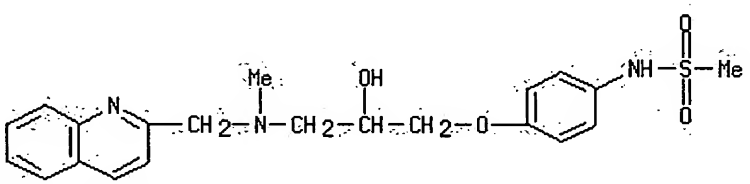
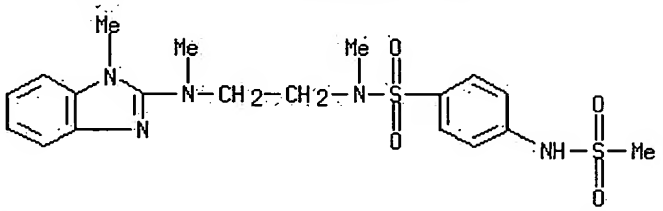
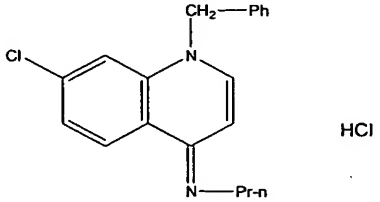
ID	Common Name	Structure Chemical Name	CAS Registry Number
118	SB 237376	 Benzamide, N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-4-nitro-	179258-59-4
119	Sematilide CK 1752 ZK 110516	 Benzamide, N-[2-(diethylamino)ethyl]-4-[(methylsulfonyl)amino]-	101526-83-4
120	Sinominine	 Morphinan-6-one, 7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methyl-, (9*α*,13*α*,14*α*)-	115-53-7
121	Sotalol	 Methanesulfonamide, N-[4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]-	No CAS RN
122	Spriadoline	 Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(5R,7S,8S)-7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]-, rel-	87151-85-7 87151-97-5

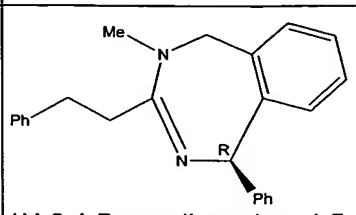
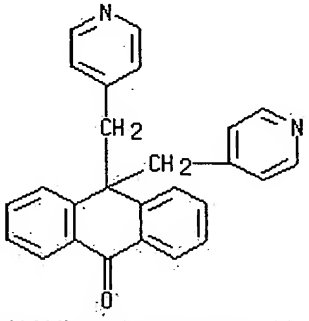
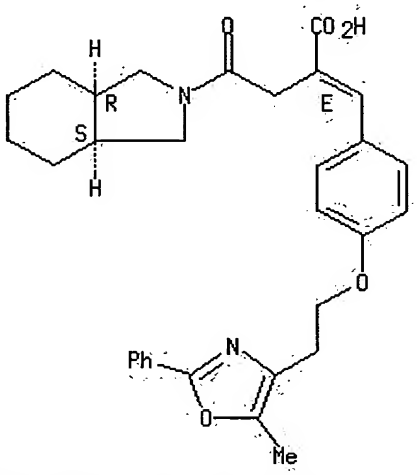
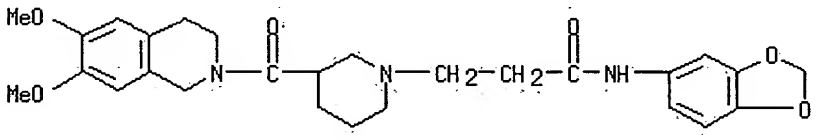
ID	Common Name	Structure Chemical Name	CAS Registry Number
123	SPM 928 ATI 2042	 2-Benzofuranacetic acid, 3-[4-[2-(diethylamino)ethoxy]-3,5-diiodobenzoyl]-, 1-methylpropyl ester	270587-33-2
124	SSR 149744B	No name available. No structure available	No CAS RN
125	Tedisamil KC 8857	 Spiro[cyclopentane-1,9'-[3,7]diazabicyclo[3.3.1]nonane], 3',7'-bis(cyclopropylmethyl)-	90961-53-8
126	Terikalant RP 62719	 Piperidine, 1-[2-[(4S)-3,4-dihydro-2H-1-benzopyran-4-yl]ethyl]-4-(3,4-dimethoxyphenyl)-	132338-79-5
127	TH 9121	 1H-Imidazol-2-amine, N-butyl-N-(2,6-dichlorophenyl)-4,5-dihydro-	53331-33-2

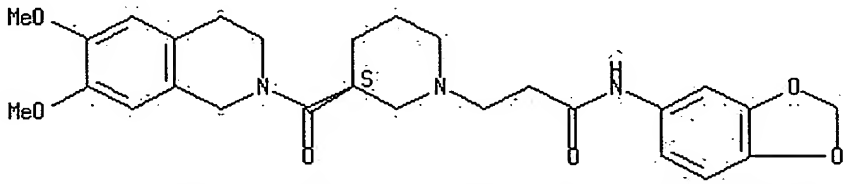
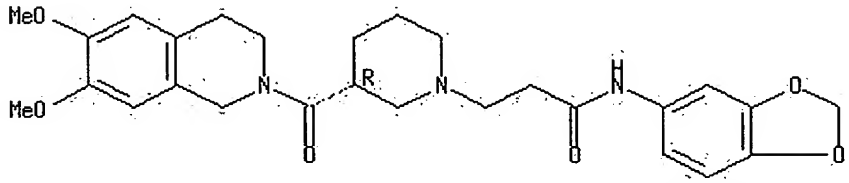
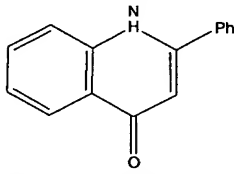
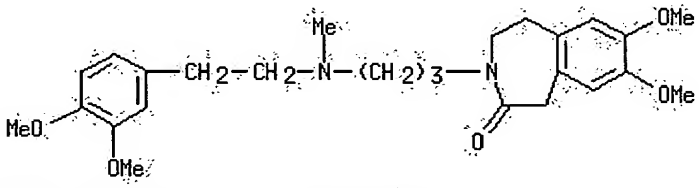
ID	Common Name	Structure Chemical Name	CAS Registry Number
128	TH 9122	 1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)-4,5-dihydro-N-4-pentenyl-	159428-97-4
129	TN 871	 Piperazine, 1-(6-butyl-6,7-dihydro-5H-indeno[5,6-d]-1,3-dioxol-5-yl)-4-methyl-, dihydrochloride	153127-39-0
130	Toxin based therapeutics BRI 6906	 No name available	No CAS RN
131	U 37883A	 4-Morpholinecarboximidamide, N-cyclohexyl-N'-tricyclo[3.3.1.13,7]dec-1-yl-, monohydrochloride	57568-80-6

ID	Common Name	Structure Chemical Name	CAS Registry Number
132	U 50488H	 Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, monomethanesulfonate	67198-13-4 83913-06-8 (salt)
133	UCL 1439	 Quinolinium, 4,4'-(1,10-decanediyldiimino)bis[2-methyl-1-(phenylmethyl)-, salt with trifluoroacetic acid (1:2)	173412-06-1
134	UCL 1530	 5,35:7,10:12,15:17,22-Tetraetheno-6H-dibenzo[b,r][1,5,16,20]tetraazacyclohentriacontine-5,17-diium, 11,16,23,24,25,26,27,28,29,30,31,32,33,34-tetradecahydro-	172998-23-1

ID	Common Name	Structure Chemical Name	CAS Registry Number
135	UCL 1559 TRAM 30	 1H-Imidazolium, 1-[(2-chlorophenyl)diphenylmethyl]-3-methyl-, iodide	215462-39-8
136	UCL 1608	 1H-Azepine, hexahydro-1-[4-[9-(phenylmethyl)-9H-fluoren-9-yl]-2-butynyl]-, ethanedioate (1:1)	371172-30-4-371172-31-5 (salt)
137	UCL 1684	 5,27:13,18:21,24-Trietheno-11,7-metheno-7H-dibenzo[b,n][1,5,12,16]tetraazacyclotricosine-5,13-diium, 6,12,19,20,25,26-hexahydro-, dibromide	199934-16-2

ID	Common Name	Structure Chemical Name	CAS Registry Number
138	UK 66914	 Methanesulfonamide, N-[4-[1-hydroxy-2-[4-(4-pyridinyl)-1-piperazinyl]ethyl]phenyl]-	113049-11-9
139	UK 78282	 Piperidine, 4-[(diphenylmethoxy)methyl]-1-[3-(4-methoxyphenyl)propyl]-	191217-42-2
140	WAY 123223	 Methanesulfonamide, N-[4-[2-hydroxy-3-[methyl(2-quinolinylmethyl)amino]propoxy]phenyl]-	136727-01-0
141	WAY 123398	 Benzenesulfonamide, N-methyl-N-[2-[methyl(1-methyl-1H-benzimidazol-2-yl)amino]ethyl]-4-[(methylsulfonyl)amino]-	138490-53-6
142	WIN 17317-3	 1-Propanamine, N-[7-chloro-1-(phenylmethyl)-4(1H)-quinolinylidene]-, monohydrochloride	169970-60-9

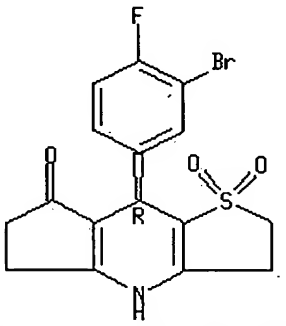
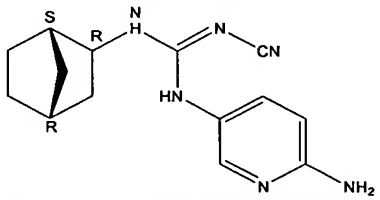
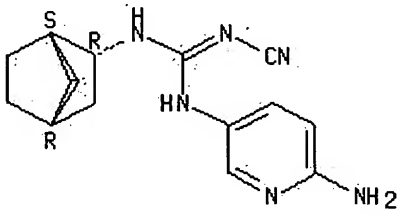
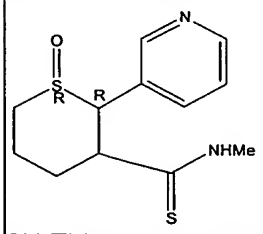
ID	Common Name	Structure Chemical Name	CAS Registry Number
143	WIN 61773	 HCl 1H-2,4-Benzodiazepine, 4,5-dihydro-4-methyl-1-phenyl-3-(2-phenylethyl)-, monohydrochloride, (1R)-	142153-24-0
144	XE 991	 9(10H)-Anthracenone, 10,10-bis(4-pyridinylmethyl)-	122955-42-4
145	Y 39677	 2H-Isoindole-2-butanoic acid, octahydro-α-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methylene]-γ-oxo, (α*E*,3aR,7aS)-rel-	312688-85-0
146	YM 19348 Racemate	 # HCl 1-Piperidinepropanamide, N-1,3-benzodioxol-5-yl-3-[(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)carbonyl]-, monohydrochloride	312737-98-7

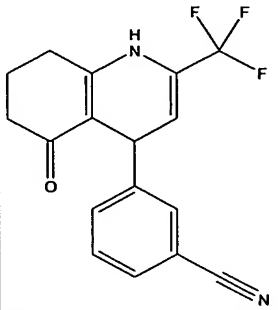
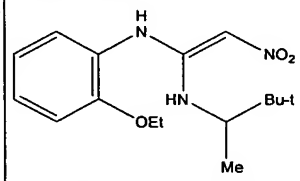
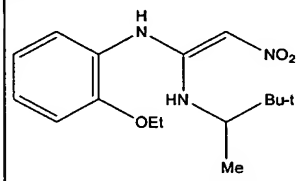
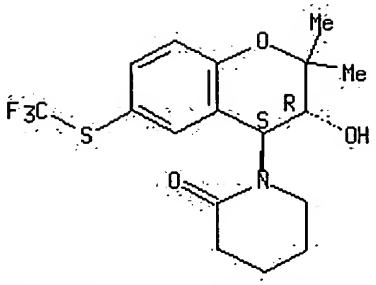
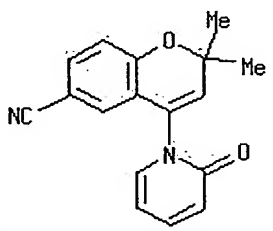
ID	Common Name	Structure Chemical Name	CAS Registry Number
147	YM 193489-S	 1-Piperidinepropanamide, N-1,3-benzodioxol-5-yl-3-[(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)carbonyl]-, (3S)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1)	312738-09-3
148	YM 193489-R	 1-Piperidinepropanamide, N-1,3-benzodioxol-5-yl-3-[(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)carbonyl]-, (3R)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1)	312738-03-7
149	YT 1	 4(1H)-Quinolinone, 2-phenyl-	14802-18-7
150	Zatebradine	 2H-3-Benzazepin-2-one, 3-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-	85175-67-3

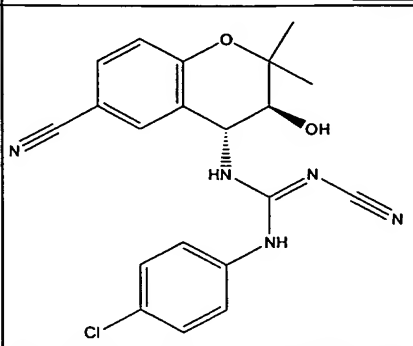
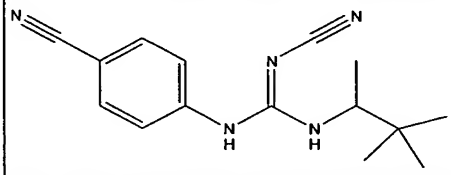
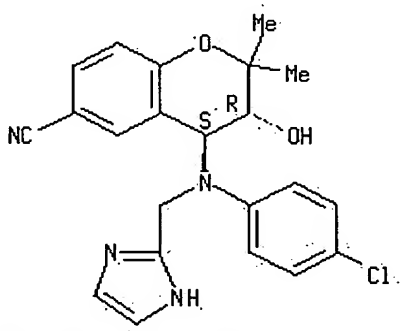
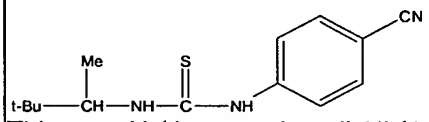
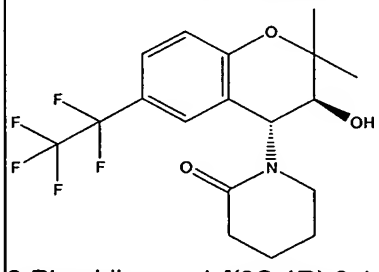
[0399] In a further embodiment, compounds that are useful for the potassium ion channel opener or a pharmaceutically acceptable salt or prodrug thereof in connection with the present invention include, but are not limited to, the compounds set forth in Table 5B below:

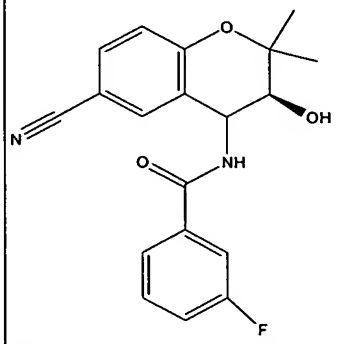
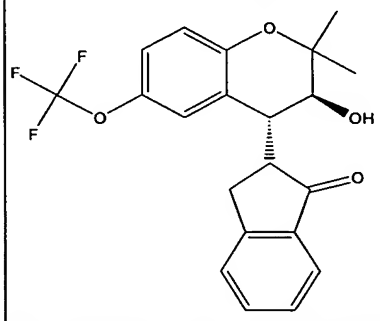
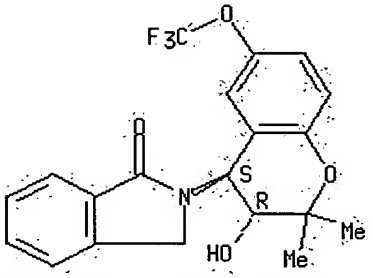
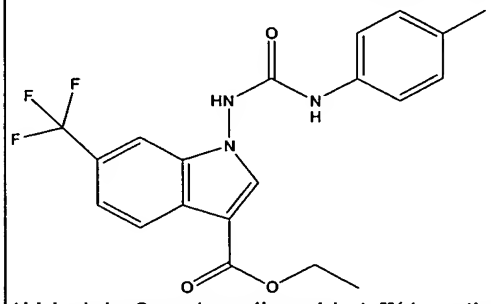
TABLE 5B

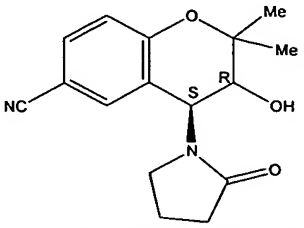
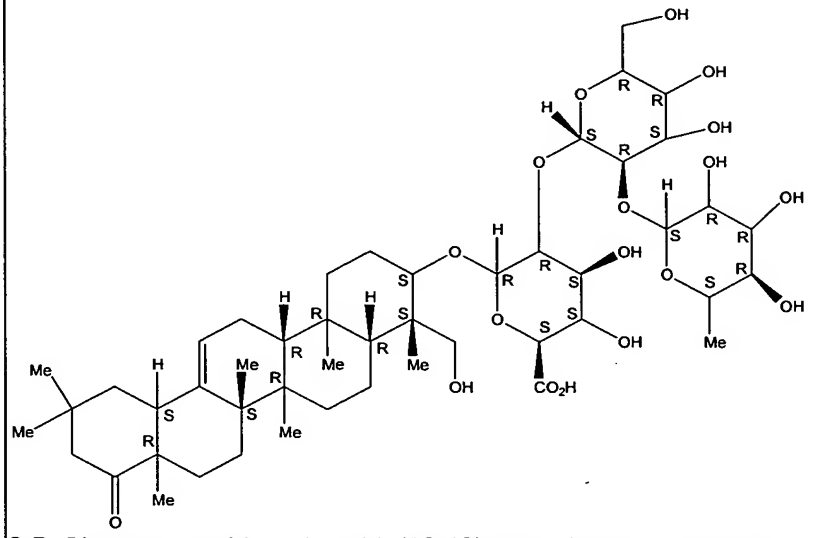
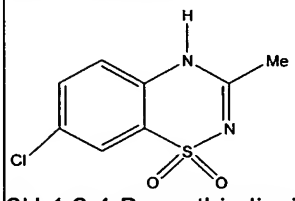
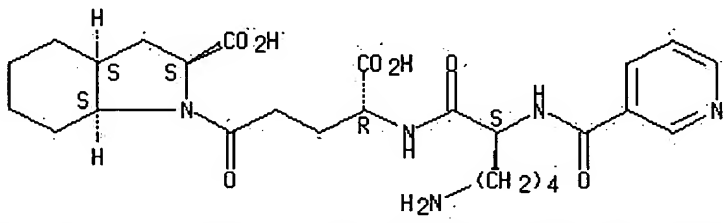
EXAMPLES OF POTASSIUM ION CHANNEL OPENERS AS EMBODIMENTS

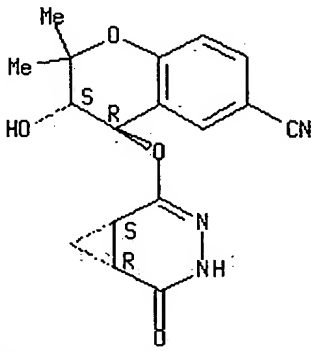
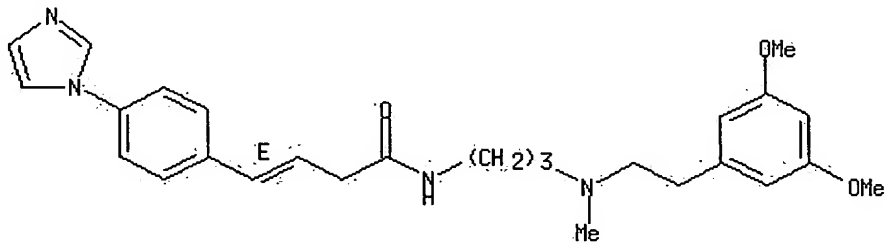
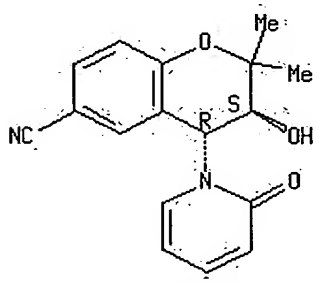
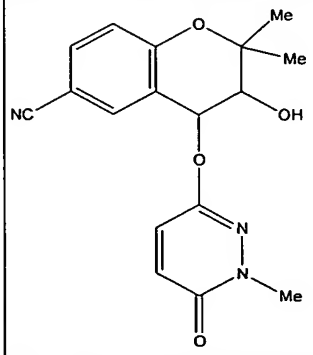
ID	Common Name	Structure Chemical Name	CAS Registry Number
1	ABA 267	No name available. No structure available	No CAS RN
2	ABT 598	 7H-Cyclopenta[b]thieno[2,3-e]pyridin-7-one, 8-(3-bromo-4-fluorophenyl)-2,3,4,5,6,8-hexahydro-, 1,1-dioxide	227609-69-0
3	AL 0670	 Guanidine, N-(6-amino-3-pyridinyl)-N'-bicyclo[2.2.1]hept-2-yl-N"-cyano-, (1S-endo)-	156473-05-1
4	AL 0671	 # HCl (+)–1–(6–Amino–3–pyridyl)–3–[(1S,2R,4R)-bicyclo[2.2.1]hept–2–yl]–2–cyanoguanidine hydrochloride	158513-06-5
5	Aprikalim	 2H-Thiopyran-2-carbothioamide, tetrahydro-N-methyl-2-(3-pyridinyl)-, 1-oxide, (1R-trans)-	132562-26-6

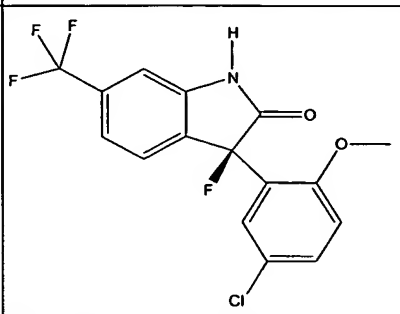
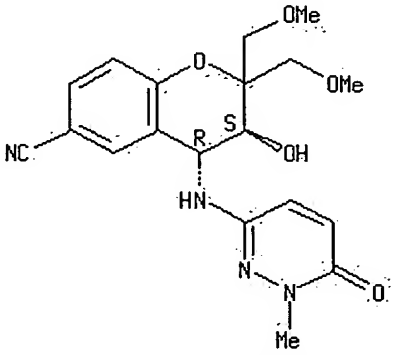
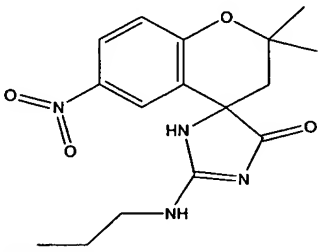
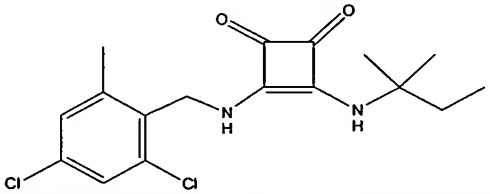
ID	Common Name	Structure Chemical Name	CAS Registry Number
6	AZD 0947	 Benzonitrile, 3-[(4S)-1,4,5,6,7,8-hexahydro-5-oxo-2-(trifluoromethyl)-4-quinolinyl]-	172649-40-0
7	BAY X 9227	 1,1-Ethenediamine, N-(2-ethoxyphenyl)-2-nitro-N'-(1,2,2-trimethylpropyl)-, (-)-	144341-32-2
8	BAY X 9228	 1,1-Ethenediamine, N-(2-ethoxyphenyl)-2-nitro-N'-(1,2,2-trimethylpropyl)-, (+)-	144341-30-0
9	BDF 9333	 2-Piperidinone, 1-[3,4-dihydro-3-hydroxy-2,2-dimethyl-6-[(trifluoromethyl)thio]-2H-1-benzopyran-4-yl]-, trans-	128150-08-3 157856-78-5 (no structure)
10	Bimakalim	 2,2-Dimethyl-4-[2-oxo-1(2H)-pyridinyl]-2H-1-benzopyran-6-carbonitrile	117545-11-6

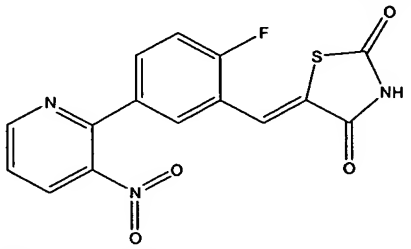
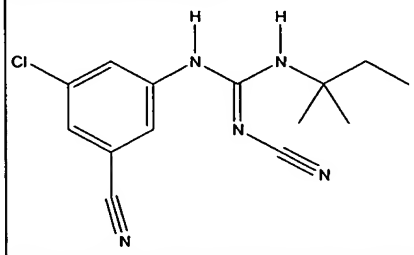
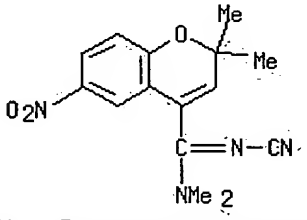
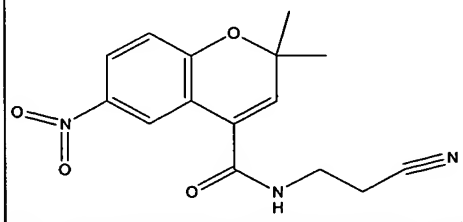
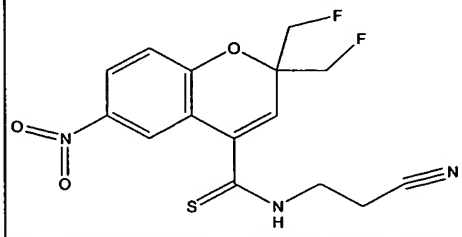
ID	Common Name	Structure Chemical Name	CAS Registry Number
11	BMS 180448	 Guanidine, N-(4-chlorophenyl)-N'-cyano-N"-[(3S,4R)-6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl]-	144301-94-0
12	BMS 182264	 Guanidine, N-cyano-N'-(4-cyanophenyl)-N"-(1,2,2-trimethylpropyl)-	127749-54-6
13	BMS 191095	 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)-	166095-21-2
14	BRL 38277		No CAS RN
15	BRL 49074	 Thiourea, N-(4-cyanophenyl)-N'-(1,2,2-trimethylpropyl)-	147752-22-5 133208-69-2 (discontinued)
16	BRL 55834	 2-Piperidinone, 1-[(3S,4R)-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-(pentafluoroethyl)-2H-1-benzopyran-4-yl]-	131899-25-7

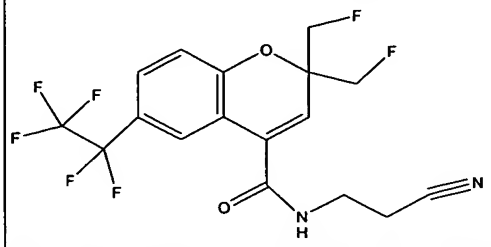
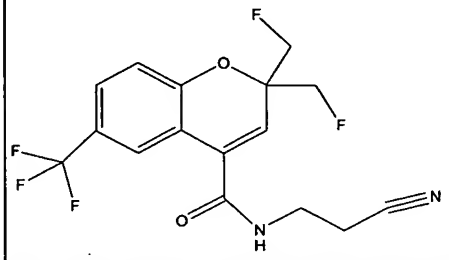
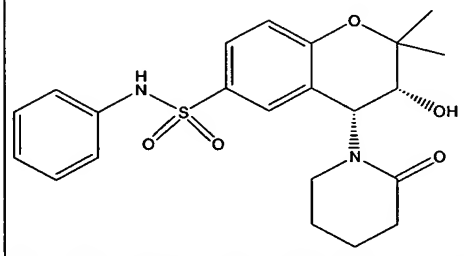
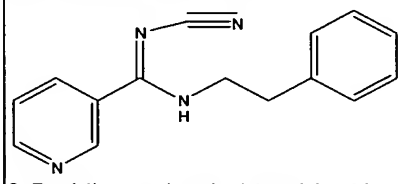
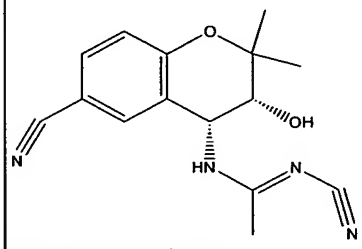
ID	Common Name	Structure Chemical Name	CAS Registry Number
17	BRL 61164	 Benzamide, N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-3-fluro-, (3R-trans)-	146986-81-4
18	Celikalim WAY 120491	 1H-Isoindol-1-one, 2-[(3S,4R)-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-(trifluoromethoxy)-2H-1-benzopyran-4-yl]-2,3-dihydro-	124916-54-7
19	Celikalim derivatives	 1H-Isoindol-1-one, 2-[3,4-dihydro-3-hydroxy-2,2-dimethyl-6-(trifluoromethoxy)-2H-1-benzopyran-4-yl]-2,3-dihydro-, trans-	124787-43-5 for example
20	CGS 7181	 1H-Indole-3-carboxylic acid, 1-[[(4-methylphenyl)amino]carbonyl]-2-hydroxy-6-(trifluoromethyl)-, ethyl ester	200345-93-3

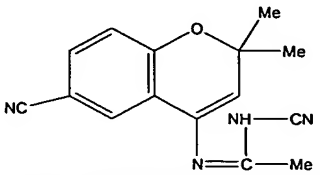
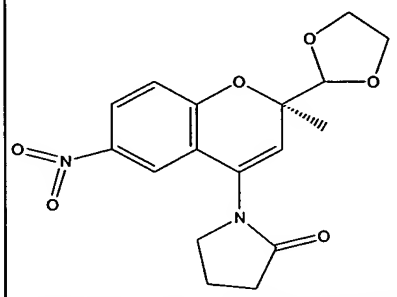
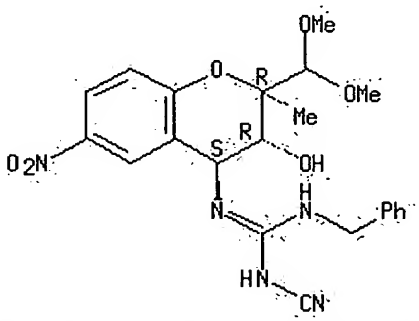
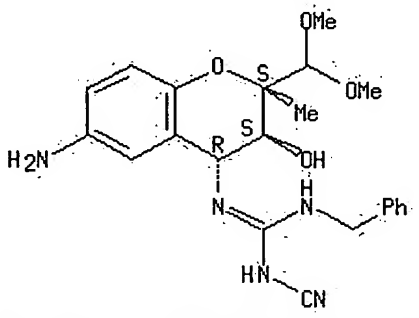
ID	Common Name	Structure Chemical Name	CAS Registry Number
21	Cromakalim BRL 34915	 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-, (3R,4S)-rel-	94470-67-4
22	Dehydrosoyasaponin 1	 β-D-Glucopyranosiduronic acid, (3β,4β)-23-hydroxy-22-oxoolean-12-en-3-yl O-6-deoxy-α-L-mannopyranosyl-(1→2)-O-β-D-galactopyranosyl-(1→2)-	117210-14-7
23	Diazoxide	 2H-1,2,4-Benzothiadiazine, 7-chloro-3-methyl-1, 1,1-dioxide	364-98-7
24	DU 1777	 1H-Indole-2-carboxylic acid, N2-(3-pyridinylcarbonyl)-L-lysyl-D-γ-glutamyloctahydro-, (2S,3aS,7aS)-	116662-73-8

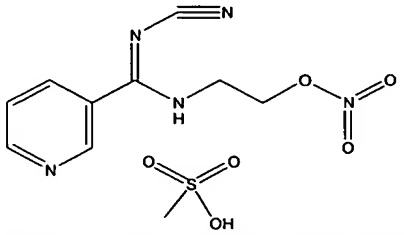
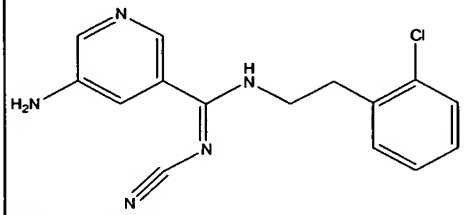
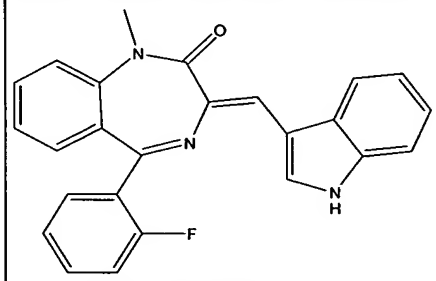
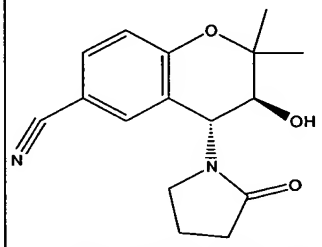
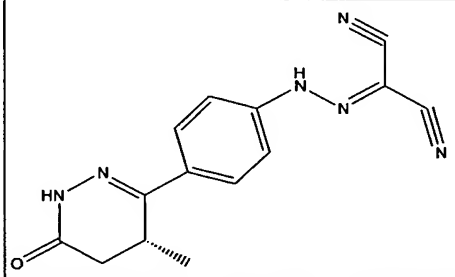
ID	Common Name	Structure Chemical Name	CAS Registry Number
25	DY 9708	 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-[[(1S,6R)-5-oxo-3,4-diazabicyclo[4.1.0]hept-2-en-2-yl]oxy]-, (3S, 4R)-	273213-70-0
26	E 4080	 # 2 HCl 3-Butenamide, N-[3-[[2-(3,5-dimethoxyphenyl)ethyl]methylamino]propyl]-4-[4-(1H-imidazol-1-yl)phenyl]-, dihydrochloride, (3E)-	127404-34-6
27	Emakalim	 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-(2-oxo-1(2H)-pyridinyl)-, (3S,4R)-	129729-66-4
28	EMD 57283	 2H-1-Benzopyran-6-carbonitrile, 4-[(1,6-dihydro-1-methyl-6-oxo-3-pyridazinyl)oxy]-3,4-dihydro-3-hydroxy-2,2-dimethyl-	134352-59-3

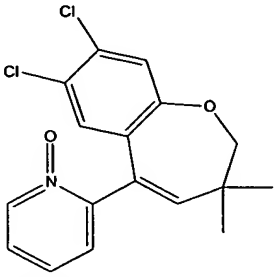
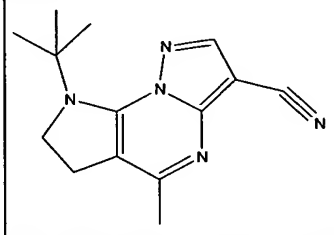
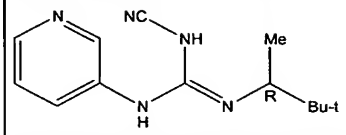
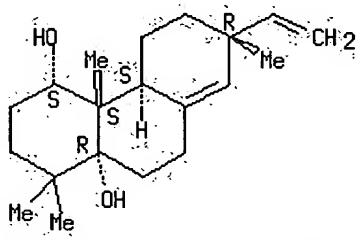
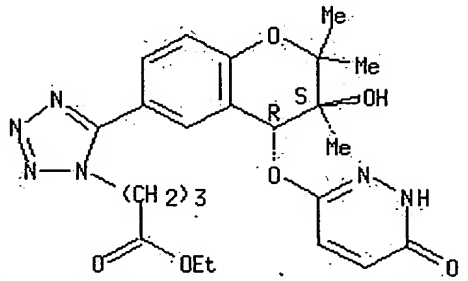
ID	Common Name	Structure Chemical Name	CAS Registry Number
29	EMD 67618	No name available. No structure available	No CAS RN
30	Flindokalner	 2H-Indol-2-one, 3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-, (3S)-	187523-35-9
31	JTV 506	 2H-1-Benzopyran-6-carbonitrile, 4-[(1,6-dihydro-1-methyl-6-oxo-3-pyridazinyl)amino]-3,4-dihydro-3-hydroxy-2,2-bis(methoxymethyl)-, (3S,4R)-	170148-29-5
32	Potassium channel openers	 Spiro[4H-1-benzopyran-4,4'-[4H]imidazol]-5'(1'H)-one, 2,3-dihydro-2,2-dimethyl-6-nitro-2'-(propylamino)-	148795-10-2
33	Potassium channel openers	 3-Cyclobutene-1,2-dione, 3-[[(2,4-dichloro-6-methylphenyl)methyl]amino]-4-[(1,1-dimethylpropyl)amino]-	202520-55-6

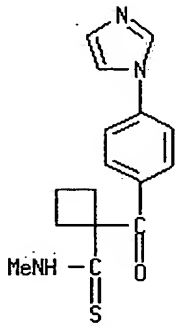
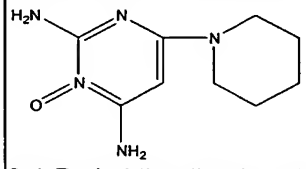
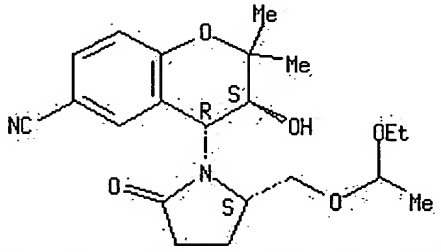
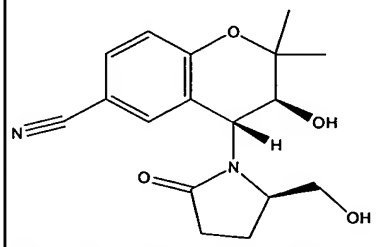
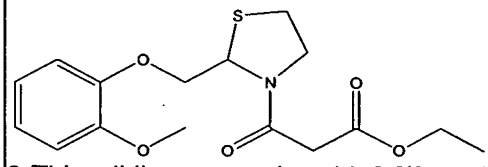
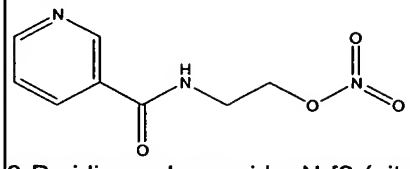
ID	Common Name	Structure Chemical Name	CAS Registry Number
34	Potassium ATP agonists	 No name available	No CAS RN
35	KB R5608	 Guanidine, N-(3-chloro-5-cyanophenyl)-N'-cyano-N"-(1,1-dimethylpropyl)-	144930-88-1
36	KC 128	 2H-1-Benzopyran-4-carboximidamide, N'-cyano-N,N,2,2-tetramethyl-6-nitro-	141591-92-6
37	KC 332	 2H-1-Benzopyran-4-carboxamide, N-(2-cyanoethyl)-2,2-dimethyl-6-nitro-	141572-31-8
38	KC 399	 2H-1-Benzopyran-4-carbothioamide, N-(2-cyanoethyl)-2,2-bis(fluoromethyl)-6-nitro-	152661-13-7

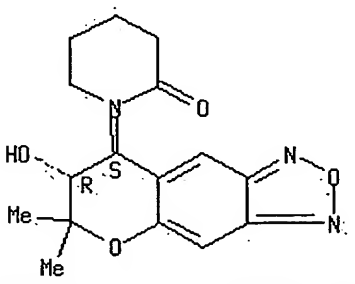
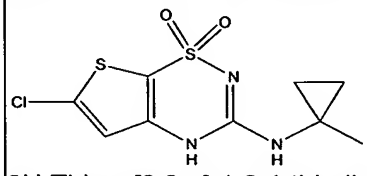
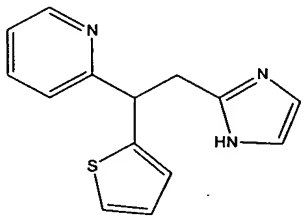
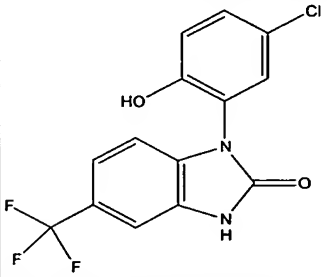
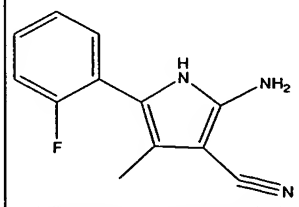
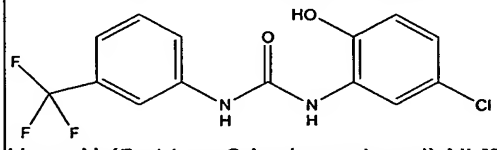
ID	Common Name	Structure Chemical Name	CAS Registry Number
39	KC 515	 2H-1-Benzopyran-4-carboxamide, N-(2-cyanoethyl)-2,2-bis(fluoromethyl)-6-(pentafluoroethyl)-	152661-26-2
40	KC 516	 2H-1-Benzopyran-4-carboxamide, N-(2-cyanoethyl)-2,2-bis(fluoromethyl)-6-(trifluoromethyl)-	152661-22-8
41	KCO 912	 2H-1-Benzopyran-6-sulfonamide, 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-piperidinyl)-N-phenyl-, (3S,4R)-	185695-83-4
42	KI 1769	 3-Pyridinecarboximidamide, N-cyano-N'-(2-phenylethyl)-	133300-00-2
43	KIL 769	Methane sulfonic acid salt of KI 1769	No CAS RN
44	KP 294	 No name available	CAS RN for enantiomer only

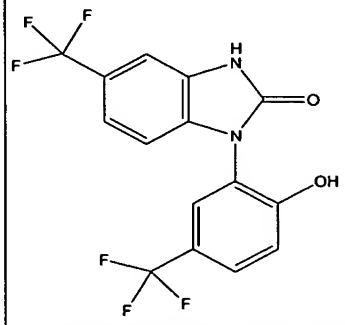
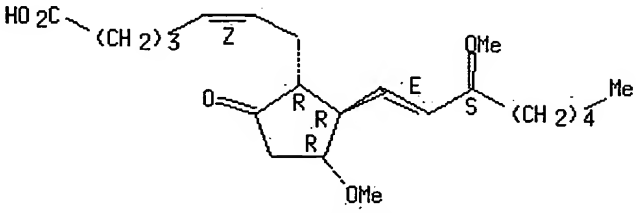
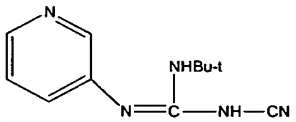
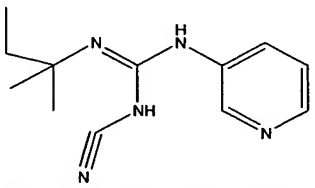
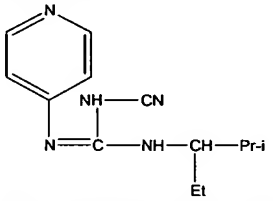
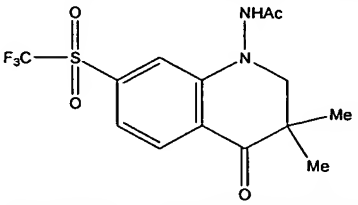
ID	Common Name	Structure Chemical Name	CAS Registry Number
45	KP 403	 Ethanimidamide, N-cyano-N'-(6-cyano-2,2-dimethyl-2H-1-benzopyran-4-yl)-	133178-25-3
46	KR 30450	 2-Pyrrolidinone, 1-[(2R)-2-(1,3-dioxolan-2-yl)-2-methyl-6-nitro-2H-1-benzopyran-4-yl]-	172489-10-0
47	KR 31372	 Guanidine, N-cyano-N'-[(2R,3R,4S)-2-(dimethoxymethyl)-3,4-dihydro-3-hydroxy-2-methyl-6-nitro-2H-1-benzopyran-4-yl]-N''-(phenylmethyl)-	327614-26-6
48	KR 31378	 Guanidine, N-[(2S,3S,4R)-6-amino-2-(dimethoxymethyl)-3,4-dihydro-3-hydroxy-2-methyl-2H-1-benzopyran-4-yl]-N'-cyano-N''-(phenylmethyl)-	335381-68-5

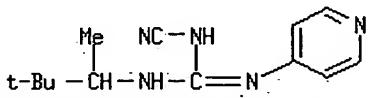
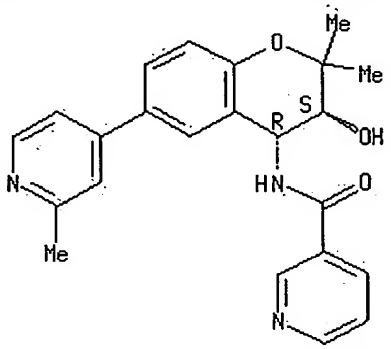
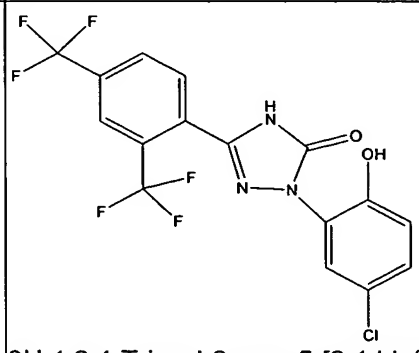
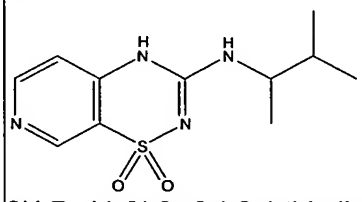
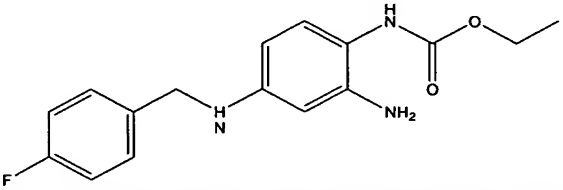
ID	Common Name	Structure Chemical Name	CAS Registry Number
49	KRN 2391	 3-Pyridinecarboximidamide, N-cyano-N'-[2-(nitrooxy)ethyl]-, monomethanesulfonate	134431-49-5
50	KRN 4884	 3-Pyridinecarboximidamide, 5-amino-N-[2-(2-chlorophenyl)ethyl]-N'-cyano-	152802-84-1
51	L-364373	 2H-1,4-Benzodiazepin-2-one, 5-(2-fluorophenyl)-1,3-dihydro-3-(1H-indol-3-ylmethyl)-1-methyl-, (3R)-	103342-82-1
52	Lemakalim Levocromakalim	 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-, (3S,4R)-	94535-50-9
53	Levosimendan	 Propanedinitrile, [[4-[(4R)-1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl]phenyl]hydrazono]-	141505-33-1

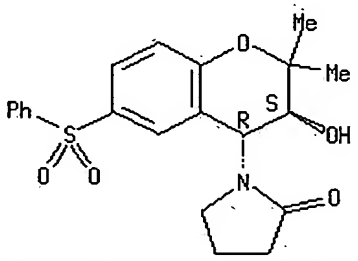
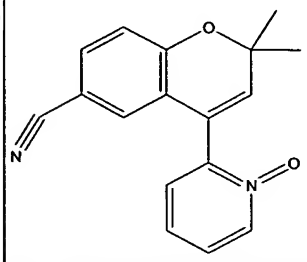
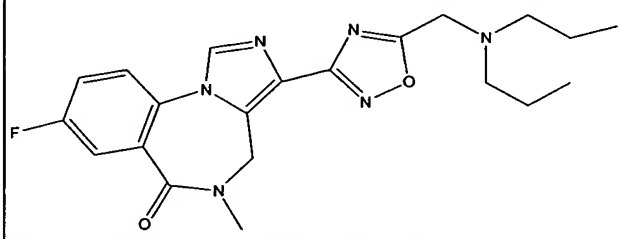
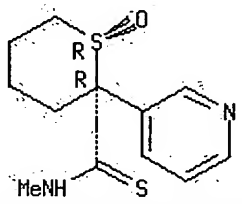
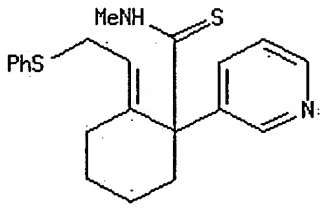
ID	Common Name	Structure Chemical Name	CAS Registry Number
54	LM 3339	 Pyridine, 2-(7,8-dichloro-2,3-dihydro-3,3-dimethyl-1-benzoxepin-5-yl)-, 1-oxide	157987-31-0
55	LP 805	 6H-Pyrazolo[1,5-a]pyrrolo[3,2-e]pyrimidine-3-carbonitrile, 8-(1,1-dimethylethyl)-7,8-dihydro-5-methyl-	129909-32-6
56	(-) LY 222675	 Guanidine, N-cyano-N'-3-pyridinyl-N"-(1,2,2-trimethylpropyl)-, (R)-	131815-93-5
57	Maxikdiol	 4,10a(1H)-Phenanthrenediol, 7-ethenyl-2,3,4,4a,4b,5,6,7,9,10-decahydro-1,1,4a,7-tetramethyl-, (4S,4aS,4bS,7R,10aR)-	161161-47-3
58	Mazokalim	 1H-Tetrazole-1-butanoic acid, 5-[(3S,4R)-4-[(1,6-dihydro-6-oxo-3-pyridazinyl)oxy]-3,4-dihydro-3-hydroxy-2,2,3-trimethyl-2H-1-benzopyran-6-yl]-, ethyl ester	1641787-54-5

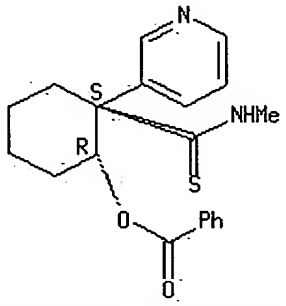
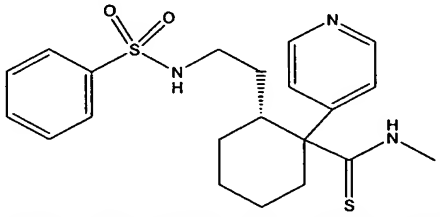
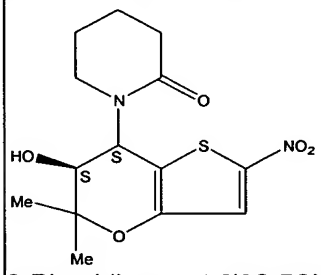
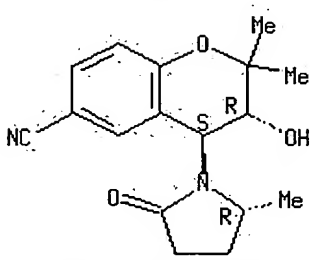
ID	Common Name	Structure Chemical Name	CAS Registry Number
59	MCC 134	 Cyclobutanecarbothioamide, 1-[4-(1H-imidazol-1-yl)benzoyl]-N-methyl-	181238-67-5
60	Minoxidil	 2,4-Pyrimidinediamine, 6-(1-piperidinyl)-, 3-oxide	38304-91-5
61	MJ 355	 2H-1-Benzopyran-6-carbonitrile, 4-[(2R)-2-[(1-ethoxyethoxy)methyl]-5-oxo-1-pyrrolidinyl]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)-rel-	252044-45-4
62	MJ 451	 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(2S)-2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]-2,2-dimethyl-, (3S,4R)-	129655-17-0
63	Moguisteine	 3-Thiazolidinepropanoic acid, 2-[(2-methoxyphenoxy)methyl]-β-oxo, ethyl ester	119637-67-1
64	Nicorandil	 3-Pyridinecarboxamide, N-[2-(nitrooxy)ethyl]-	65141-46-0

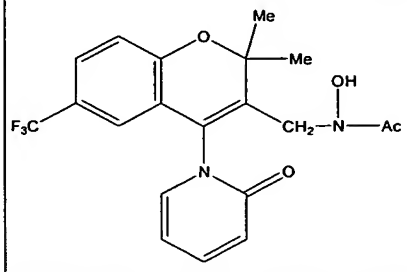
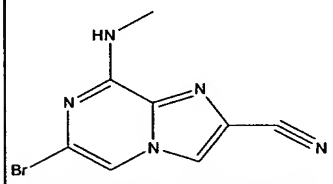
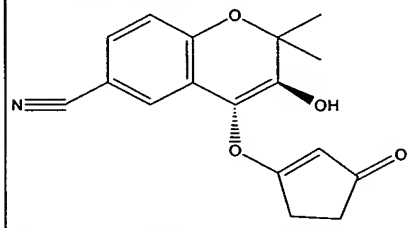
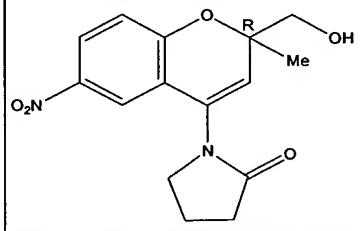
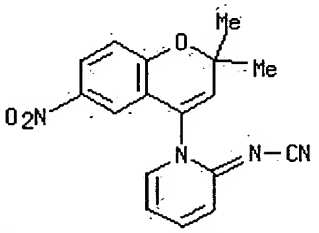
ID	Common Name	Structure Chemical Name	CAS Registry Number
65	NIP 121	 2-Piperidinone, 1-[(7R,8S)-7,8-dihydro-7-hydroxy-6,6-dimethyl-6H-pyrano[2,3-f]-2,1,3-benzoxadiazol-8-yl]-, rel-(+)-	135244-62-1
66	NN 414	 2H-Thieno[3,2-e]-1,2,4-thiadiazin-3-amine, 6-chloro-N-(1-methylcyclopropyl)-, 1,1-dioxide	279215-43-9
67	NN 5501	 Pyridine, 2-[2-(1H-imidazol-2-yl)-1-(2-thienyl)ethyl]-	142338-70-3
68	NS 004	 2H-Benzimidazol-2-one, 1-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-5-(trifluoromethyl)-	141797-92-4
69	NS 8	 1H-Pyrrole-3-carbonitrile, 2-amino-5-(2-flurophenyl)-4-methyl-	186033-14-7
70	NS 1608	 Urea, N-(5-chloro-2-hydroxyphenyl)-N'-[3-(trifluoromethyl)phenyl]	160383-80-2

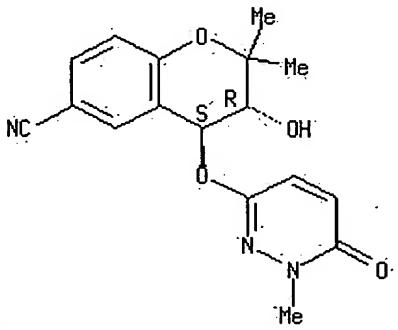
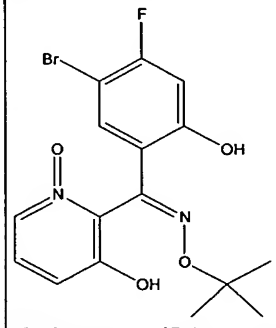
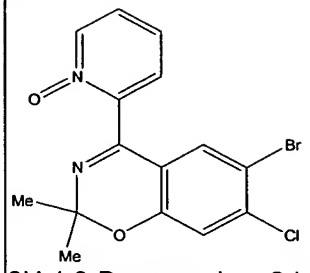
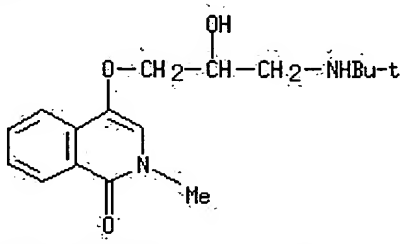
ID	Common Name	Structure Chemical Name	CAS Registry Number
71	NS 1619	 2H-Benzimidazol-2-one,1,3-dihydro-1-[2-hyroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-	153587-01-0
72	ONO AE 248	 Prosta-5,13-dien-1-oic acid, 11,15-dimethoxy-9-oxo-, (5Z,11α,13E,15S)-	211230-67-0
73	P 1060	 Guanidine, N-cyano-N'-(1,1-dimethylethyl)-N"-3-pyridinyl-	60559-94-6
74	P 1075	 Guanidine, N-cyano-N'-(1,1-dimethylpropyl)-N"-3-pyridinyl-	60559-98-0
75	P 1188	 Guanidine, N-cyano-N'-(1-ethyl-2-methylpropyl)-N"-4-pyridinyl-	67026-48-6
76	PC 286	 Acetamide, N-[3,4-dihydro-3,3-dimethyl-4-oxo-7-[(trifluoromethyl)sulfonyl]-1(2H)-quinolinyl]-	174777-09-4

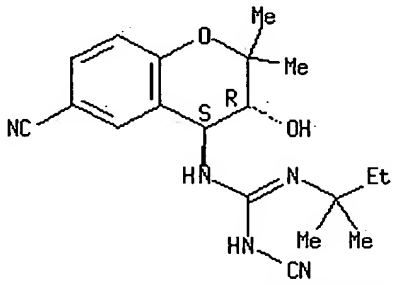
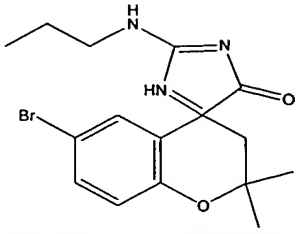
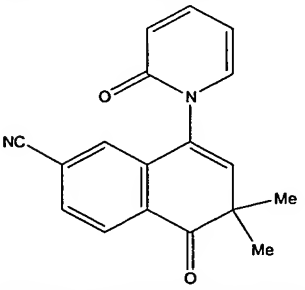
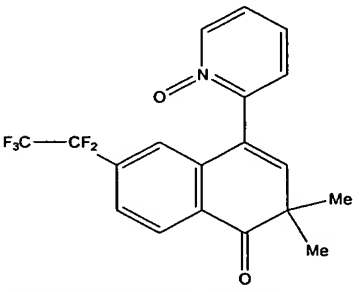
ID	Common Name	Structure Chemical Name	CAS Registry Number
77	Pinacidil P 1134	 Guanidine, N-cyano-N'-4-pyridinyl-N"-(1,2,2-trimethylpropyl)-	60560-33-0
78	PKF 217	 3-Pyridinecarboxamide, N-[(3S,4R)-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-(2-methyl-4-pyridinyl)-2H-1-benzopyran-4-yl]-	359440-17-8
79	PM 56D8	No name available. No structure available	NO CAS RN related to 129929-86-8
80	PNU 83757	No name available. No structure available	443795-79-7
81	Potassium Channel Opener	 3H-1,2,4-Triazol-3-one, 5-[2,4-bis(trifluoromethyl)phenyl]-2-(5-chloro-2-hydroxyphenyl)-1,2-dihydro-	202822-25-1
82	Potassium Channel Opener BPDZ44	 2H-Pyrido[4,3-e]-1,2,4-thiadiazin-3-amine, N-(1,2-dimethylpropyl)-, 1,1-dioxide	152382-67-7
83	Retigabine D 23129	 Carbamic acid, [2-amino-4-[[(4-fluorophenyl)methyl]amino]phenyl]-, ethyl ester	150812-12-7

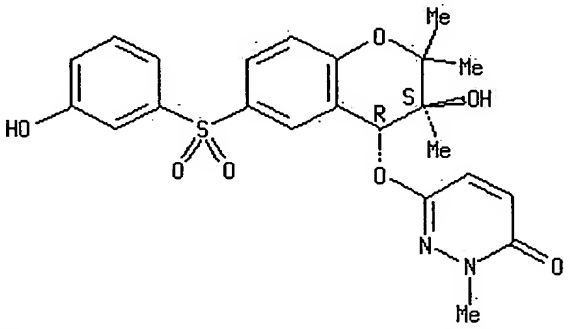
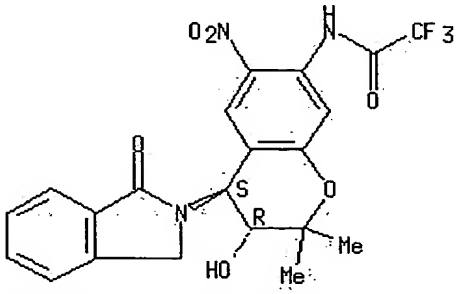
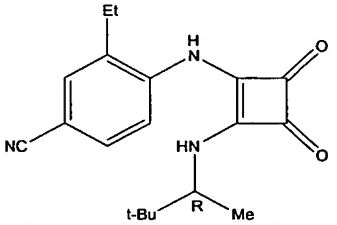
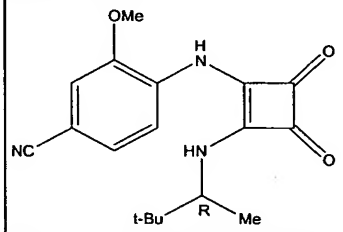
ID	Common Name	Structure Chemical Name	CAS Registry Number
84	Rilmakalim Rimakalim HOE 234	 2-Pyrrolidinone, 1-[(3S,4R)-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-(phenylsulfonyl)-2H-1-benzopyran-4-yl]-	132014-21-2
85	RO 31-6930	 2H-1-Benzopyran-6-carbonitrile, 2,2-dimethyl-4-(1-oxido-2-pyridinyl)-	120280-37-7
86	RO 48-6791	 6H-Imidazo[1,5-a][1,4]benzodiazepin-6-one, 3-[5-[(dipropylamino)methyl]-1,2,4-oxadiazol-3-yl]-8-fluoro-4,5-dihydro-5-methyl-	172407-17-9
87	RP 49356 Enantiomer of aprikalim	 2H-Thiopyran-2-carbothioamide, tetrahydro-N-methyl-2-(3-pyridinyl)-, 1-oxide, (1R,2R)-rel-	89544-10-5
88	RP 66266	 Cyclohexanecarbothioamide, N-methyl-2-[2-(phenylthio)ethylidene]-1-(3-pyridinyl)-	131332-13-3

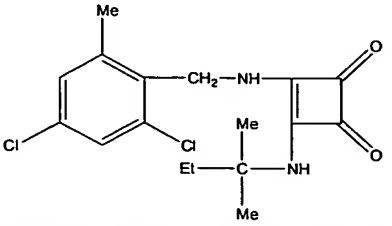
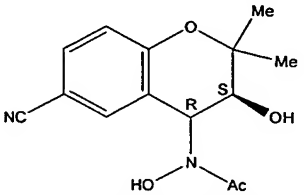
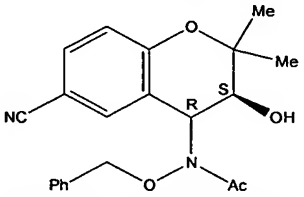
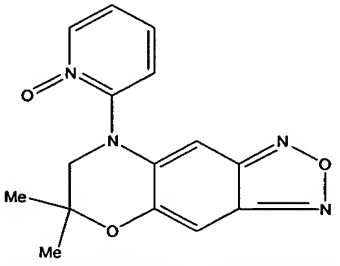
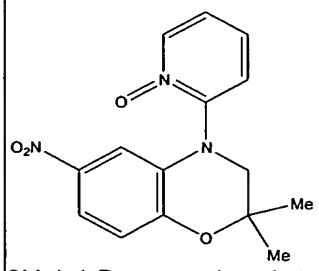
ID	Common Name	Structure Chemical Name	CAS Registry Number
89	RP 66471	 Cyclohexanecarbothioamide, 2-(benzoyloxy)-N-methyl-1-(3-pyridinyl)-, (1S,2R)-	133320-02-2
90	RP 66784	 Cyclohexanecarbothioamide, N-methyl-2-[2-[(phenylsulfonyl) amino]ethyl]-1-(3-pyridinyl)-, trans- (+/-)	137392-34-8
91	RWJ 29009	 2-Piperidinone, 1-[(6S,7S)-6,7-dihydro-6-hydroxy-5,5-dimethyl-2-nitro-5H-thieno[3,2-b]pyran-7-yl]-	143164-10-7
92	S 0121	 2H-1-Benzopryan-6-carbonitrile, 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-[(2R)-2-methyl-5-oxo-1-pyrrolidinyl]- (3R,4S)-	118366-03-3
93	S 103	No name available. No structure available	227765-58-4

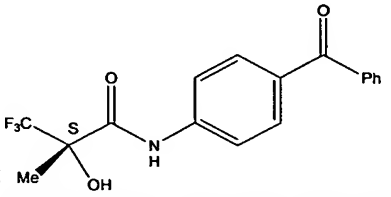
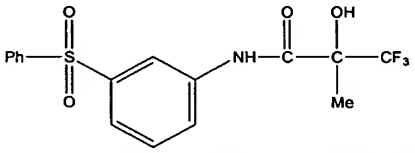
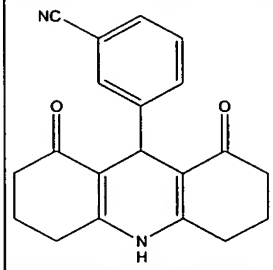
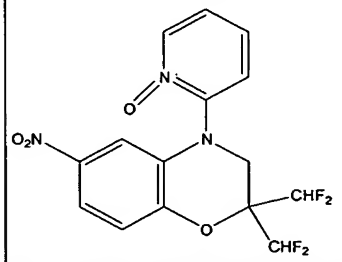
ID	Common Name	Structure Chemical Name	CAS Registry Number
94	Sarakalim	 Acetamide, N-[[2,2-dimethyl-4-(2-oxo-1(2H)-pyridinyl)-6-(trifluoromethyl)-2H-1-benzopyran-3-yl]methyl]-N-hydroxy-	148430-28-8
95	SCA 40	 Imidazo[1,2-a]pyrazine-2-carbonitrile, 6-bromo-8-(methylamino)-	142744-39-6
96	SDZ PCO 400	 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-2,2-dimethyl-4-[(3-oxo-1-cyclopenten-1-yl)oxy]-, (3S,4R)-	121055-10-5
97	SKP 818	 2-Pyrrolidinone, 1-[(2R)-2-(hydroxymethyl)-2-methyl-6-nitro-2H-1-benzopyran-4-yl]-	189832-98-2
98	SR 47063	 Cyanamide, [1-(2,2-dimethyl-6-nitro-2H-1-benzopyran-4-yl)-2(1H)-pyridinylidene)-	135809-60-8

ID	Common Name	Structure Chemical Name	CAS Registry Number
99	Symakalim	 2H-1-Benzopyran-6-carbonitrile, 4-[(1,6-dihydro-1-methyl-6-oxo-3-pyridazinyl)oxy]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, trans-	129421-71-2 (no stereochemistry around OH 134352-59-3 (EMD 57283) is trans (+/-)
100	TAK 636	 Methanone, (5-bromo-4-fluoro-2-hydroxyphenyl)(3-hydroxy-1-oxido-2-pyridinyl)-, O-(1,1-dimethylethyl)oxime, (Z)-	162267-74-5
101	TCV 925	 2H-1,3-Benzoxazine, 6-bromo-7-chloro-2,2-dimethyl-4-(1-oxido-2-pyridinyl)-	142304-17-4
102	Tilisolol	 1(2H)-Isoquinolinone, 4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-2-methyl-	85136-71-6

ID	Common Name	Structure Chemical Name	CAS Registry Number
103	U 89232	 Guanidine, N-cyano-N'-[(3R,4S)-6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl]-N''-(1,1-dimethylpropyl)-, rel-	134017-78-0
104	U 99751	 Spiro[4H-1-benzopyran-4,4'-[4H]imidazol]-5'(1'H)-one, 6-bromo-2,3-dihydro-2,2-dimethyl-2'-(propylamino)-, (S)-	171858-84-7
105	UR 8218	No name available. No structure available	No CAS RN
106	UR 8225	 2-Naphthalenecarbonitrile, 5,6-dihydro-6,6-dimethyl-5-oxo-8-(2-oxo-1(2H)-pyridinyl)-	149455-36-7
107	UR 8267		
108	UR 8308		
109	UR 8328	 1(2H)-Naphthalenone, 2,2-dimethyl-4-(1-oxido-2-pyridinyl)-6-(pentafluoroethyl)-	158662-59-0

ID	Common Name	Structure Chemical Name	CAS Registry Number
110	UK 157147	 3(2H)-Pyridazinone, 6-[[(3S,4R)-3,4-dihydro-3-hydroxy-6-[(3-hydroxyphenyl)sulfonyl]-2,2,3-trimethyl-2H-1-benzopyran-4-yl]oxy]-2-methyl-	162704-20-3
111	WAY 124903	 Acetamide, N-[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-nitro-2H-1-benzopyran-7-yl]-2,2,2-trifluoro-, trans-	129196-34-5
112	WAY 133537	 Benzonitrile, 4-[[3,4-dioxo-2-[[(1R)-1,2,2-trimethylpropyl]amino]-1-cyclobuten-1-yl]amino]-3-ethyl-	177476-74-3
113	WAY 135201	 Benzonitrile, 4-[[3,4-dioxo-2-[[(1R)-1,2,2-trimethylpropyl]amino]-1-cyclobuten-1-yl]amino]-3-methoxy-	177476-77-6

ID	Common Name	Structure Chemical Name	CAS Registry Number
114	WAY 151616	 3-Cyclobutene-1,2-dione, 3-[[(2,4-dichloro-6-methylphenyl)methyl] amino]-4-[(1,1-dimethylpropyl)amino]-	202520-55-6
115	Y 26763	 Acetamide, N-[(3S,4R)-6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl]-N-hydroxy	127408-31-5
116	Y 27152	 Acetamide, N-[(3S,4R)-6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl]-N-(phenylmethoxy)-	127408-30-4
117	YM 099	 6H-[1,2,5]Oxadiazolo[3,4-g][1,4]benzoxazine, 7,8-dihydro-6,6-dimethyl-8-(1-oxido-2-pyridinyl)-	144293-65-2
118	YM 934	 2H-1,4-Benzoxazine, 3,4-dihydro-2,2-dimethyl-6-nitro-4-(1-oxido-2-pyridinyl)-	136544-11-1

ID	Common Name	Structure Chemical Name	CAS Registry Number
119	ZD 6169	 Propanamide, N-(4-benzoylphenyl)-3,3,3-trifluoro-2-hydroxy-2-methyl-,	147696-46-6
120	ZM 226600	 Propanamide, 3,3,3-trifluoro-2-hydroxy-2-methyl-N-[3-(phenylsulfonyl)phenyl]-	183723-10-6
121	ZM 244085	 Benzonitrile, 3-(1,2,3,4,5,6,7,8,9,10-decahydro-1,8-dioxo-9-acridinyl)-	149398-59-4
122	ZM 260384	 2H-1,4-Benzoxazine, 2,2-bis(difluoromethyl)-3,4-dihydro-6-nitro-4-(1-oxido-2-pyridinyl)-	161229-62-5

[0400] Generally speaking, the pharmacokinetics of the particular agent to be administered will dictate the most preferred method of administration and dosing regiment. The potassium ion channel modulator can be administered as a pharmaceutical composition with or without a carrier. The terms "pharmaceutically acceptable carrier" or a "carrier" refer to any generally acceptable excipient or drug delivery composition that is relatively inert and non-toxic. Exemplary carriers include sterile water, salt solutions (such as Ringer's solution), alcohols, gelatin, talc, viscous paraffin, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, calcium carbonate, carbohydrates

(such as lactose, sucrose, dextrose, mannose, albumin, starch, cellulose, silica gel, polyethylene glycol (PEG), dried skim milk, rice flour, magnesium stearate, and the like. Suitable formulations and additional carriers are described in Remington's Pharmaceutical Sciences, (17.sup.th Ed., Mack Pub. Co., Easton, Pa.). Such preparations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, preservatives and/or aromatic substances and the like which do not deleteriously react with the active compounds. Typical preservatives can include, potassium sorbate, sodium metabisulfite, methyl paraben, propyl paraben, thimerosal, etc. The compositions can also be combined where desired with other active substances, e.g., enzyme inhibitors, to reduce metabolic degradation.

[0401] Moreover, the potassium ion channel modulator can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The method of administration can dictate how the composition will be formulated. For example, the composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, or magnesium carbonate.

[0402] In another embodiment, the potassium ion channel modulator can be administered intravenously, parenterally, intramuscular, subcutaneously, orally, nasally, topically, by inhalation, by implant, by injection, or by suppository. For enteral or mucosal application (including via oral and nasal mucosa), particularly suitable are tablets, liquids, drops, suppositories or capsules. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Liposomes, microspheres, and microcapsules are available and can be used. Pulmonary administration can be accomplished, for example, using any of various delivery devices known in the art such as an inhaler. See. e.g. S. P. Newman (1984) in Aerosols and the Lung, Clarke and Davis (eds.), Butterworths, London, England, pp. 197-224; PCT Publication No. WO 92/16192; PCT Publication No. WO 91/08760. For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions,

emulsions, or implants, including suppositories. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-polyoxypropylene block polymers, and the like.

[0403] The actual effective amounts of compound or drug can and will vary according to the specific composition being utilized, the mode of administration and the age, weight and condition of the subject. Dosages for a particular individual subject can be determined by one of ordinary skill in the art using conventional considerations. But in general, the amount of potassium ion channel modulator will be between about 0.5 to about 1000 milligrams per day and more typically, between about 2.5 to about 750 milligrams per day and even more typically, between about 5.0 to about 500 milligrams per day. The daily dose can be administered in one to four doses per day.

[0404] By way of example, in one embodiment when the potassium ion channel modulator is nicorandil administered in a controlled release dosage form, the amount administered daily is typically from about 5 to about 40 milligrams per day administered in two doses per day. In an alternative of this embodiment, when the potassium ion channel modulator is fampridine administered in a controlled release dosage form, the amount administered is also from about 10 to about 80 milligrams per day, administered in two doses per day.

[0405] Generally speaking, the potassium ion channel modulator and cyclooxygenase-2 selective inhibitor are administered to the subject as soon as possible after the reduction in blood flow to the central nervous system in order to reduce the extent of ischemic damage. Typically, the potassium ion channel modulator and cyclooxygenase-2 selective inhibitor are administered within 10 days after the reduction of blood flow to the central nervous system and more typically, within 24 hours. In still another embodiment, the potassium ion channel modulator and cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours after the reduction in blood flow to the central nervous system. In another embodiment, the potassium ion channel modulator and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours after the reduction in blood flow to the central nervous system. In still another embodiment, the potassium ion channel modulator and cyclooxygenase-2

selective inhibitor are administered in less than about 4 hours after the reduction in blood flow to the central nervous system. In yet a further embodiment, the potassium ion channel modulator and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours after the reduction in blood flow to the central nervous system.

[0406] Moreover, the timing of the administration of the cyclooxygenase-2 selective inhibitor in relation to the administration of the potassium ion channel modulator may also vary from subject to subject. In one embodiment, the cyclooxygenase-2 selective inhibitor and potassium ion channel modulator may be administered substantially simultaneously, meaning that both agents may be administered to the subject at approximately the same time. For example, the cyclooxygenase-2 selective is administered during a continuous period beginning on the same day as the beginning of the potassium ion channel modulator and extending to a period after the end of the potassium ion channel modulator. Alternatively, the cyclooxygenase-2 selective inhibitor and potassium ion channel modulator may be administered sequentially, meaning that they are administered at separate times during separate treatments. In one embodiment, for example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning prior to administration of the potassium ion channel modulator and ending after administration of the potassium ion channel modulator. Of course, it is also possible that the cyclooxygenase-2 selective inhibitor may be administered either more or less frequently than the potassium ion channel modulator. Moreover, it will be apparent to those skilled in the art that it is possible, and perhaps desirable, to combine various times and methods of administration in the practice of the present invention.

COMBINATION THERAPIES

[0407] Generally speaking, it is contemplated that the composition employed in the practice of the invention may include one or more of any of the cyclooxygenase-2 selective inhibitors detailed above in combination with one or more of any of the potassium ion channel modulators detailed above. By way of a non-limiting example, Table 6a details a number of suitable combinations that are useful in the methods and compositions of the current invention. The combination

may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors or potassium ion channel modulators listed in Table 6a.

TABLE 6a

Cyclooxygenase-2 Selective Inhibitor	**Potassium Ion Channel Modulator**
a compound having formula I	dendrotoxin
a compound having formula I	apamin
a compound having formula I	clotrimazole
a compound having formula I	tolbutamide
a compound having formula I	glipizide
a compound having formula I	pinacidil
a compound having formula I	nicorandil
a compound having formula I	nategliniide
a compound having formula I	levcromakalim
a compound having formula I	glyburide
a compound having formula II	dendrotoxin
a compound having formula II	apamin
a compound having formula II	clotrimazole
a compound having formula II	tolbutamide
a compound having formula II	glipizide
a compound having formula II	pinacidil
a compound having formula II	nicorandil
a compound having formula II	nategliniide
a compound having formula II	levcromakalim
a compound having formula II	glyburide
a compound having formula III	dendrotoxin
a compound having formula III	apamin
a compound having formula III	clotrimazole
a compound having formula III	tolbutamide
a compound having formula III	glipizide
a compound having formula III	pinacidil
a compound having formula III	nicorandil
a compound having formula III	nategliniide
a compound having formula III	levcromakalim
a compound having formula III	glyburide
a compound having formula IV	dendrotoxin
a compound having formula IV	apamin
a compound having formula IV	clotrimazole
a compound having formula IV	tolbutamide
a compound having formula IV	glipizide
a compound having formula IV	pinacidil
a compound having formula IV	nicorandil
a compound having formula IV	nategliniide
a compound having formula IV	levcromakalim

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
a compound having formula IV	glyburide
a compound having formula V	dendrotoxin
a compound having formula V	apamin
a compound having formula V	clotrimazole
a compound having formula V	tolbutamide
a compound having formula V	glipizide
a compound having formula V	pinacidil
a compound having formula V	nicorandil
a compound having formula V	nateglinide
a compound having formula V	levcromakalim
a compound having formula V	glyburide

[0408] By way of further example, Table 6b details a number of suitable combinations that may be employed in the methods and compositions of the present invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors or potassium ion channel modulators listed in Table 6b.

Table 6b

Cyclooxygenase-2 Selective Inhibitor	**Potassium Ion Channel Modulator**
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	dendrotoxin

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	apamin

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	clotrimazole

Cyclooxygenase-2 Selective Inhibitor	**Potassium Ion Channel Modulator**
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	tolbutamide

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	glipizide

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	pinacidil

Cyclooxygenase-2 Selective Inhibitor	**Potassium Ion Channel Modulator**
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	nicorandil

Cyclooxygenase-2 Selective Inhibitor	**Potassium Ion Channel Modulator**
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	nategliniide

Cyclooxygenase-2 Selective Inhibitor	**Potassium Ion Channel Modulator**
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	levcromakalim

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, B-252	glyburide

[0409] By way of yet further example, Table 6c details additional suitable combinations that may be employed in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors or potassium ion channel modulators listed in Table 6c.

TABLE 6c

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
Celecoxib	dendrotoxin
Celecoxib	apamin
Celecoxib	clotrimazole
Celecoxib	tolbutamide
Celecoxib	glipizide
Celecoxib	pinacidil
Celecoxib	nicorandil
Celecoxib	nategliniide
Celecoxib	levcromakalim
Celecoxib	glyburide
Deracoxib	dendrotoxin
Deracoxib	apamin
Deracoxib	clotrimazole
Deracoxib	tolbutamide
Deracoxib	glipizide
Deracoxib	pinacidil
Deracoxib	nicorandil
Deracoxib	nategliniide
Deracoxib	levcromakalim
Deracoxib	glyburide
Valdecoxib	dendrotoxin
Valdecoxib	apamin
Valdecoxib	clotrimazole
Valdecoxib	tolbutamide
Valdecoxib	glipizide
Valdecoxib	pinacidil
Valdecoxib	nicorandil
Valdecoxib	nategliniide
Valdecoxib	levcromakalim
Valdecoxib	glyburide
Rofecoxib	dendrotoxin
Rofecoxib	apamin
Rofecoxib	clotrimazole
Rofecoxib	tolbutamide
Rofecoxib	glipizide
Rofecoxib	pinacidil
Rofecoxib	nicorandil
Rofecoxib	nategliniide
Rofecoxib	levcromakalim
Rofecoxib	glyburide
Etoricoxib	dendrotoxin
Etoricoxib	apamin
Etoricoxib	clotrimazole

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
Etoricoxib	tolbutamide
Etoricoxib	glipizide
Etoricoxib	pinacidil
Etoricoxib	nicorandil
Etoricoxib	nategliniide
Etoricoxib	levcromakalim
Etoricoxib	glyburide
Meloxicam	dendrotoxin
Meloxicam	apamin
Meloxicam	clotrimazole
Meloxicam	tolbutamide
Meloxicam	glipizide
meloxicam	pinacidil
meloxicam	nicorandil
meloxicam	nategliniide
meloxicam	levcromakalim
meloxicam	glyburide
Parecoxib	dendrotoxin
Parecoxib	apamin
Parecoxib	clotrimazole
Parecoxib	tolbutamide
Parecoxib	glipizide
Parecoxib	pinacidil
Parecoxib	nicorandil
Parecoxib	nategliniide
Parecoxib	levcromakalim
Parecoxib	glyburide
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	dendrotoxin
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	apamin
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	clotrimazole
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	tolbutamide
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	glipizide
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	pinacidil
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	nicorandil
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	nategliniide
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	levcromakalim
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	glyburide

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	dendrotoxin
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	apamin
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	clotrimazole
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	tolbutamide
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	glipizide
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	pinacidil
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	nicorandil
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	nategliniide
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	levcromakalim
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	glyburide
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	dendrotoxin
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	apamin
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	clotrimazole
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	tolbutamide
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	glipizide
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	pinacidil
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	nicorandil
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	nategliniide
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	levcromakalim

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	glyburide
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	dendrotoxin
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	apamin
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	clotrimazole
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	tolbutamide
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	glipizide
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	pinacidil
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	nicorandil
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	nategliniide
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	levcromakalim
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	glyburide
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	dendrotoxin
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	apamin
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	clotrimazole

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	tolbutamide
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	glipizide
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	pinacidil
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	nicorandil
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	nategliniide
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	levcromakalim
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	glyburide
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	dendrotoxin
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	apamin
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	clotrimazole
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	tolbutamide
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	glipizide
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	pinacidil
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	nicorandil
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	nategliniide
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	levcromakalim
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	glyburide
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	dendrotoxin
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	apamin

Cyclooxygenase-2 Selective Inhibitor	Potassium Ion Channel Modulator
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	clotrimazole
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	tolbutamide
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	glipizide
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	pinacidil
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	nicorandil
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	nategliniide
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	levcromakalim
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	glyburide
lumiracoxib	dendrotoxin
lumiracoxib	apamin
lumiracoxib	clotrimazole
lumiracoxib	tolbutamide
lumiracoxib	glipizide
lumiracoxib	pinacidil
lumiracoxib	nicorandil
lumiracoxib	nategliniide
lumiracoxib	levcromakalim
lumiracoxib	glyburide

DIAGNOSIS OF A VASO-OCCLUSION

[0410] One aspect of the invention encompasses diagnosing a subject in need of treatment or prevention for a vaso-occlusive event. A number of suitable methods for diagnosing a vaso-occlusion may be used in the practice of the invention. In one such method, ultrasound may be employed. This method examines the blood flow in the major arteries and veins in the arms and legs with the use of ultrasound (high-frequency sound waves). In one embodiment, the test may combine Doppler® ultrasonography, which uses audio measurements to "hear" and measure the blood flow and duplex ultrasonography, which provides a visual image. In an alternative embodiment, the test may utilize multifrequency ultrasound or multifrequency transcranial Doppler® (MTCD) ultrasound.

[0411] Another method that may be employed encompasses injection of the subject with a compound that can be imaged. In one alternative of this embodiment, a small amount of radioactive material is injected into the subject

and then standard techniques that rely on monitoring blood flow to detect a blockage, such as magnetic resonance direct thrombus imaging (MRDTI), may be utilized to image the vaso-occlusion. In an alternative embodiment, ThromboView® (commercially available from Agenix Limited) uses a clot-binding monoclonal antibody attached to a radiolabel. In addition to the methods identified herein, a number of other suitable methods known in the art for diagnosis of vaso-occlusive events may be utilized.

INDICATIONS TO BE TREATED

[0412] Generally speaking, the composition comprising a therapeutically effective amount of a cyclooxygenase-2 selective inhibitor and a therapeutically effective amount of a potassium ion channel modulator may be employed to treat any condition resulting from a reduction in blood flow to the central nervous system.

[0413] In some aspects, the invention provides a method to treat a central nervous system cell to prevent damage in response to a decrease in blood flow to the cell. Typically the severity of damage that may be prevented will depend in large part on the degree of reduction in blood flow to the cell and the duration of the reduction. By way of example, the normal amount of perfusion to brain gray matter in humans is about 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs when the flow of blood falls below approximately 8-10 mL/100 g of brain tissue/min, while at slightly higher levels (i.e. 20-35 mL/100 g of brain tissue/min) the tissue remains alive but not able to function. In one embodiment, apoptotic or necrotic cell death may be prevented. In still a further embodiment, ischemic-mediated damage, such as cytoxic edema or central nervous system tissue anoxemia, may be prevented. In each embodiment, the central nervous system cell may be a spinal cell or a brain cell.

[0414] Another aspect encompasses administrating the composition to a subject to treat a central nervous system ischemic condition. Any central nervous system ischemic condition may be treated by the composition of the invention. In one embodiment, the ischemic condition is a stroke that results in any type of ischemic central nervous system damage, such as apoptotic or necrotic cell

death, cytoxic edema or central nervous system tissue anoxemia. The stroke may impact any area of the brain or be caused by any etiology commonly known to result in the occurrence of a stroke. In one alternative of this embodiment, the stroke is a brain stem stroke. Generally speaking, brain stem strokes strike the brain stem, which control involuntary life-support functions such as breathing, blood pressure, and heartbeat. In another alternative of this embodiment, the stroke is a cerebellar stroke. Typically, cerebellar strokes impact the cerebellum area of the brain, which controls balance and coordination. In still another embodiment, the stroke is an embolic stroke. In general terms, embolic strokes may impact any region of the brain and typically result from the blockage of an artery by a vaso-occlusion. In yet another alternative, the stroke may be a hemorrhagic stroke. Like embolic strokes, hemorrhagic stroke may impact any region of the brain, and typically result from a ruptured blood vessel characterized by a hemorrhage (bleeding) within or surrounding the brain. In a further embodiment, the stroke is a thrombotic stroke. Typically, thrombotic strokes result from the blockage of a blood vessel by accumulated deposits.

[0415] In another embodiment, the ischemic condition may result from a disorder that occurs in a part of the subject's body outside of the central nervous system, but yet still causes a reduction in blood flow to the central nervous system. These disorders may include, but are not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, a myocardial infarction, a transient ischemic attack, unstable angina, or sickle cell anemia. Moreover, the central nervous system ischemic condition may occur as result of the subject undergoing a surgical procedure. By way of example, the subject may be undergoing heart surgery, lung surgery, spinal surgery, brain surgery, vascular surgery, abdominal surgery, or organ transplantation surgery. The organ transplantation surgery may include heart, lung, pancreas or liver transplantation surgery. Moreover, the central nervous system ischemic condition may occur as a result of a trauma or injury to a part of the subject's body outside the central nervous system. By way of example the trauma or injury may cause a degree of bleeding that significantly reduces the total volume of blood in the subject's body. Because of this reduced total volume, the amount of blood flow to the central nervous system is concomitantly reduced. By way of further example, the trauma

or injury may also result in the formation of a vaso-occlusion that restricts blood flow to the central nervous system.

[0416] Of course it is contemplated that the composition may be employed to treat any central nervous system ischemic condition irrespective of the cause of the condition. In one embodiment, the ischemic condition results from a vaso-occlusion. The vaso-occlusion may be any type of occlusion, but is typically a cerebral thrombosis or a cerebral embolism. In a further embodiment, the ischemic condition may result from a hemorrhage. The hemorrhage may be any type of hemorrhage, but is generally a cerebral hemorrhage or a subararachnoid hemorrhage. In still another embodiment, the ischemic condition may result from the narrowing of a vessel. Generally speaking, the vessel may narrow as a result of a vasoconstriction such as occurs during vasospasms, or due to arteriosclerosis. In yet another embodiment, the ischemic condition results from an injury to the brain or spinal cord.

[0417] In yet another aspect, the composition is administered to reduce infarct size of the ischemic core following a central nervous system ischemic condition. Moreover, the composition may also be beneficially administered to reduce the size of the ischemic penumbra or transitional zone following a central nervous system ischemic condition

[0418] In addition to a cyclooxygenase-2 selective inhibitor and a potassium ion channel modulator, the composition of the invention may also include any agent that ameliorates the effect of a reduction in blood flow to the central nervous system. In one embodiment, the agent is an anticoagulant including thrombin inhibitors such as heparin and Factor Xa inhibitors such as warafin. In another embodiment, the agent is a thrombolytic agent including tissue plasminogen activator, urokinase, desmoteplase (vampire bat plasminogen activator). In an additional embodiment, the agent is an anti-platelet inhibitor such as a GP IIb/IIIa inhibitor. Additional agents include but are not limited to, HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrizol; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; vitamin B_6 (also

known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); β-adrenergic receptor blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

[0419] In a further aspect, the composition may be employed to reverse or lessen central nervous system cell damage following a traumatic brain or spinal cord injury. Traumatic brain or spinal cord injury may result from a wide variety of causes including, for example, blows to the head or back from objects; penetrating injuries from missiles, bullets, and shrapnel; falls; skull fractures with resulting penetration by bone pieces; and sudden acceleration or deceleration injuries. The composition of the invention may be beneficially utilized to treat the traumatic injury irrespective of its cause.

[0420] The composition may also beneficially be employed to increase recovery of neural cell function following brain or spinal cord injury. Generally speaking, when neurons are lost due to disease or trauma, they are not replaced. Rather, the remaining neurons must adapt to whatever loss occurred by altering their function or functional relationship relative to other neurons. Following injury, neural tissue begins to produce trophic repair factors, such as nerve growth factor and neuron cell adhesion molecules, which retard further degeneration and promote synaptic maintenance and the development of new synaptic connections. But, as the lost cells are not replaced, existing cells must take over some of the functions of the missing cells, i.e., they must "learn" to do something new. In part, recovery of function from brain traumatic damage involves plastic changes that occur in brain structures other than those damaged. Indeed, in many cases, recovery from brain damage represents the taking over by healthy brain regions of the functions of the damaged area. Thus the composition of the present invention may be administered to facilitate learning of new functions by uninjured brain areas to compensate for the loss of function by other regions.

EXAMPLES

[0421] A combination therapy of a COX-2 selective inhibitor and a potassium ion channel modulator for the treatment or prevention of a vaso-

occlusive event or a related disorder in a subject can be evaluated as described in the following tests detailed below.

[0422] A particular combination therapy comprising a potassium ion channel modulator and a COX-2 inhibitor can be evaluated in comparison to a control treatment such as a placebo treatment, administration of a COX-2 inhibitor only, or administration of a potassium ion channel modulator only. By way of example, a combination therapy may contain any of the potassium ion channel modulators and COX-2 inhibitors detailed in the present invention, including the combinations set forth in Tables 6a, 6b, or 6c may be tested as a combination therapy. The dosages of a potassium ion channel modulator and COX-2 inhibitor in a particular therapeutic combination may be readily determined by a skilled artisan conducting the study. The length of the study treatment will vary on a particular study and can also be determined by one of ordinary skill in the art. By way of example, the combination therapy may be administered for 4 weeks. The potassium ion channel modulator and COX-2 inhibitor can be administered by any route as described herein, but are preferably administered orally for human subjects.

EXAMPLE 1-Evaluation of COX-1 and COX-2 activity *in vitro*

[0423] The COX-2 inhibitors suitable for use in this invention exhibit selective inhibition of COX-2 over COX-1 when tested *in vitro* according to the following activity assays.

PREPARATION OF RECOMBINANT COX BACULOVIRUSES

[0424] Recombinant COX-1 and COX-2 are prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses are isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells ($2x10^8$) along with 200 ng of linearized baculovirus plasmid DNA by the calcium

phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer (10^7-10^8 pfu/mL) stocks of virus are prepared. For large scale production, SF9 insect cells are infected in 10 liter fermentors (0.5 x 106/mL) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet is homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80°C before being assayed for COX activity.

ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0425] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

FAST ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0426] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 µM phenol, 1 µM heme, 300 µM epinephrine) with the addition of 20 µl of 100 µM arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after two minutes at 37°C by transferring 40 µl of

reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. Indomethacin, a non-selective COX-2/COX-1 inhibitor, may be utilized as a positive control. The PGE_2 formed is typically measured by standard ELISA technology utilizing a PGE2 specific antibody, available from a number of commercial sources.

[0427] Each compound to be tested may be individually dissolved in 2 ml of dimethyl sulfoxide (DMSO) for bioassay testing to determine the COX-1 and COX-2 inhibitory effects of each particular compound. Potency is typically expressed by the IC_{50} value expressed as g compound/ml solvent resulting in a 50% inhibition of PGE2 production. Selective inhibition of COX-2 may be determined by the IC_{50} ratio of COX-1/COX-2.

[0428] By way of example, a primary screen may be performed in order to determine particular compounds that inhibit COX-2 at a concentration of 10 ug/ml. The compound may then be subjected to a confirmation assay to determine the extent of COX-2 inhibition at three different concentrations (e.g., 10 ug/ml, 3.3 ug/ml and 1.1 ug/ml). After this screen, compounds can then be tested for their ability to inhibit COX-1 at a concentration of 10 ug/ml. With this assay, the percentage of COX inhibition compared to control can be determined, with a higher percentage indicating a greater degree of COX inhibition. In addition, the IC_{50} value for COX-1 and COX-2 can also be determined for the tested compound. The selectivity for each compound may then be determined by the IC_{50} ratio of COX-1/COX-2, as set-forth above.

EXAMPLE 2-METHODS FOR MEASURING PLATELET AGGREGATION AND PLATELET ACTIVATION MARKERS

[0429] The following studies can be performed in human subjects or laboratory animal models, such as mice. Prior to the initiation of a clinical study involving human subjects, the study should be approved by the appropriate Human Subjects Committee and subjects should be informed about the study and give written consent prior to participation.

[0430] Platelet activation can be determined by a number of tests available in the art. Several such tests are described below. In order to determine the effectiveness of the treatment, the state of platelet activation is evaluated at several time points during the study, such as before administering

the combination treatment and once a week during treatment. The exemplary procedures for blood sampling and the analyses that can be used to monitor platelet aggregation are listed below.

PLATELET AGGREGATION STUDY

[0431] Blood samples are collected from an antecubital vein via a 19-gauge needle into two plastic tubes. Each sample of free flowing blood is collected through a fresh venipuncture site distal to any intravenous catheters using a needle and Vacutainer hood into 7 cc vacutainer tubes (one with CTAD (dipyridamole), and the other with 3.8% trisodium citrate). If blood is collected simultaneously for any other studies, it is preferable that the platelet sample be obtained second or third, but not first. If only the platelet sample is collected, the initial 2-3 cc of blood is discharged and then the vacutainer tube is filled. The venipuncture is adequate if the tube fills within 15 seconds. All collections are performed by trained personnel.

[0432] After the blood samples for each subject have been collected into two Vacutainer tubes, they are immediately, but gently, inverted 3 to 5 times to ensure complete mixing of the anticoagulant. Tubes are not shaken. The Vacutainer tubes are filled to capacity, since excess anticoagulant can alter platelet function. Attention is paid to minimizing turbulence whenever possible. Small steps, such as slanting the needle in the Vacutainer to have the blood run down the side of tube instead of shooting all the way to the bottom, can result in significant improvement. These tubes are kept at room temperature and transferred directly to the laboratory personnel responsible for preparing the samples. The Vacutainer tubes are not chilled at any time.

[0433] Trisodium citrate (3.8%) and whole blood is immediately mixed in a 1:9 ratio, and then centrifuged at 1200 g for 2.5 minutes, to obtain platelet-rich plasma (PRP), which is kept at room temperature for use within 1 hour for platelet aggregation studies. Platelet count is determined in each PRP sample with a Coulter Counter ZM (Coulter Co., Hialeah, Fla.). Platelet numbers are adjusted to 3.50×10^{8} /ml for aggregation with homologous platelet-poor plasma. PRP and whole blood aggregation tests are performed simultaneously. Whole blood is diluted 1:1 with the 0.5 ml PBS, and then swirled gently to mix. The cuvette with

the stirring bar is placed in the incubation well and allowed to warm to 37°C for 5 minutes. Then the samples are transferred to the assay well. An electrode is placed in the sample cuvette. Platelet aggregation is stimulated with 5 μM ADP, 1 μg/ml collagen, and 0.75 mM arachidonic acid. All agonists are obtained, e.g., from Chronolog Corporation (Hawertown, Pa.). Platelet aggregation studies are performed using a Chrono-Log Whole Blood Lumi-Aggregometer (model 560-Ca). Platelet aggregability is expressed as the percentage of light transmittance change from baseline using platelet-poor plasma as a reference at the end of recording time for plasma samples, or as a change in electrical impedance for whole blood samples. Aggregation curves are recorded for 4 minutes and analyzed according to internationally established standards using Aggrolink® software.

[0434] Aggregation curves of subjects receiving a combination therapy containing a potassium ion channel modulator and a COX-2 inhibitor can then be compared to the aggregation curves of subjects receiving a control treatment in order to determine the efficacy of said combination therapy.

WASHED PLATELETS FLOW CYTOMETRY

[0435] Venous blood (8 ml) is collected in a plastic tube containing 2 ml of acid-citrate-dextrose (ACD) (7.3 g citric acid, 22.0 g sodium citrate x $2H_2O$ and 24.5 glucose in 1000 ml distilled water) and mixed well. The blood-ACD mixture is centrifuged at 1000 r.p.m. for 10 minutes at room temperature. The upper 2/3 of the platelet-rich plasma (PRP) is then collected and adjusted to pH=6.5 by adding ACD. The PRP is then centrifuged at 3000 r.p.m. for 10 minutes. The supernatant is removed and the platelet pellet is gently resuspended in 4 cc of the washing buffer (10 mM Tris/HCl, 0.15 M NaCl, 20 mM EDTA, pH=7.4). Platelets are washed in the washing buffer, and in TBS (10 mM Tris, 0.15 M NaCl, pH=7.4). All cells are then divided into the appropriate number of tubes. By way of example, if 9 different surface markers are evaluated, as described herein, then the cells should be divided into ten tubes, such that nine tubes containing washed platelets are incubated with 5 μl fluorescein isothiocyanate (FITC)-conjugated antibodies in the dark at +4°C for 30 minutes, and one tube remains unstained and serves as a negative control. Surface antigen expression is measured with monoclonal

murine anti-human antibodies, such as CD9 (p24); CD41a (IIb/IIIa, aIIbb3); CD42b (Ib); CD61(IIIa) (DAKO Corporation, Carpinteria, Calif.); CD49b (VLA-2, or a2b1); CD62p (P-selectin); CD31 (PECAM-1); CD 41b (IIb); and CD51/CD61 (vitronectin receptor, avb3) (PharMingen, San Diego Calif.), as the expression of these antigens on the cells is associated with platelet activation. After incubation, the cells are washed with TBS and resuspended in 0.25 ml of 1% paraformaldehyde. Samples are stored in the refrigerator at +4°C, and analyzed on a Becton Dickinson FACScan flow cytometer with laser output of 15 mw, excitation at 488 nm, and emission detection at 530+-30 nm. The data can be collected and stored in list mode, and then analyzed using CELLQuest® software. FACS procedures are described in detail in, e.g., Gurbel, P. A. et al., *J Amer Coll Cardiol* 31: 1466-1473 (1998); Serebruany, V. L. et al., *Am Heart J* 136: 398-405 (1998); Gurbel, P. A. et al., *Coron Artery Dis* 9: 451-456 (1998) and Serebruany, V. L. et al., *Arterioscl Thromb Vasc Biol* 19: 153-158 (1999).

[0436] The antibody staining of platelets isolated from subjects receiving a combination therapy can then be compared to the staining of platelets isolated from subjects receiving a control treatment in order to determine the effect of the combination therapy on platelets.

WHOLE BLOOD FLOW CYTOMETRY

[0437] Four cc of blood is collected in a tube, containing 2 cc of acid-citrate-dextrose (ACD, see previous example) and mixed well. The buffer, TBS (10 mM Tris, 0.15 M NaCl, pH 7.4) and the following fluorescein isothiocyanate (FITC) conjugated monoclonal antibodies (PharMingen, San Diego, Calif., USA, and DAKO, Calif., USA) are removed from a refrigerator and allowed to warm at room temperature (RT) prior to their use. The non-limiting examples of antibodies that can be used include CD41 (IIb/IIIa), CD31 (PECAM-1), CD62p (P-selectin), and CD51/61 (Vitronectin receptor). For each subject, six amber tubes (1.25 ml) are one Eppendorf tube (1.5 ml) are obtained and marked appropriately. 450 μl of TBS buffer is pipetted to the labeled Eppendorf tube. A patient's whole blood tube is inverted gently twice to mix, and 50 μl of whole blood is pipetted to the appropriately labeled Eppendorf tube. The Eppendorf tube is capped and the diluted whole blood is mixed by inverting the Eppendorf tube gently two times,

followed by pipetting 50 μl of diluted whole blood to each amber tube. 5 μl of appropriate antibody is pipetted to the bottom of the corresponding amber tube. The tubes are covered with aluminum foil and incubated at 4°C for 30 minutes. After incubation, 400 μl of 2% buffered paraformaldehyde is added. The amber tubes are closed with a lid tightly and stored in a refrigerator at 4°C until the flow cytometric analysis. The samples are analyzed on a Becton Dickinson FACScan flow cytometer. These data are collected in list mode files and then analyzed. As mentioned in (B.), the antibody staining of platelets isolated from subjects receiving a combination therapy can then be compared to the staining of platelets isolated from subjects receiving a control treatment.

ELISA

[0438] Enzyme-linked immunosorbent assays (ELISA) are used according to standard techniques and as described herein. Eicosanoid metabolites may be used to determine platelet aggregation. The metabolites are analyzed due to the fact that eicosanoids have a short half-life under physiological conditions. Thromboxane B2 (TXB_2), the stable breakdown product of thromboxane A_2 and 6keto-PGF_1 alpha, the stable degradation product of prostacyclin may be tested. Thromboxane B2 is a stable hydrolysis product of TXA_2 and is produced following platelet aggregation induced by a variety of agents, such as thrombin and collagen. 6keto-prostaglandin F_1 alpha is a stable hydrolyzed product of unstable PGI_2 (prostacyclin). Prostacyclin inhibits platelet aggregation and induces vasodilation. Thus, quantitation of prostacyclin production can be made by determining the level of 6keto-PGF_1. The metabolites may be measured in the platelet poor plasma (PPP), which is kept at -4°C. Also, plasma samples may also be extracted with ethanol and then stored at –80° C before final prostaglandin determination, using, e.g., TiterZymes® enzyme immunoassays according to standard techniques (PerSeptive Diagnostics, Inc., Cambridge, Mass., USA). ELISA kits for measuring TXB_2 and 6keto-PGF_1 are also commercially available.

[0439] The amounts of TXB_2 and 6keto-PGF_1 in plasma of subjects receiving a combination therapy and subjects receiving a control therapy can be compared to determine the efficacy of the combination treatment.

CLOSURE TIME MEASURED WITH THE DADE BEHRING PLATELET FUNCTION ANALYZER, PFA-100®

[0440] PFA-100® can be used as an *in vitro* system for the detection of platelet dysfunction. It provides a quantitative measure of platelet function in anticoagulated whole blood. The system comprises a microprocessor-controlled instrument and a disposable test cartridge containing a biologically active membrane. The instrument aspirates a blood sample under constant vacuum from the sample reservoir through a capillary and a microscopic aperture cut into the membrane. The membrane is coated with collagen and epinephrine or adenosine 5'-diphosphate. The presence of these biochemical stimuli, and the high shear rates generated under the standardized flow conditions, result in platelet attachment, activation, and aggregation, slowly building a stable platelet plug at the aperture. The time required to obtain full occlusion of the aperture is reported as the "closure time," which normally ranges from one to three minutes.

[0441] The membrane in the PFA-100® test cartridge serves as a support matrix for the biological components and allows placement of the aperture. The membrane is a standard nitrocellulose filtration membrane with an average pore size of 0.45 μm. The blood entry side of the membrane was coated with 2 μg of fibrillar Type I equine tendon collagen and 10 μg of epinephrine bitartrate or 50 μg of adenosine 5'-diphosphate (ADP). These agents provide controlled stimulation to the platelets as the blood sample passes through the aperture. The collagen surface also served as a well-defined matrix for platelet deposition and attachment.

[0442] The principle of the PFA-100® test is very similar to that described by Kratzer and Born (Kratzer, et al., *Haemostasis* 15: 357-362 (1985)). The test utilizes whole blood samples collected in 3.8% of 3.2% sodium citrate anticoagulant. The blood sample is aspirated through the capillary into the cup where it comes in contact with the coated membrane, and then passes through the aperture. In response to the stimulation by collagen and epinephrine or ADP present in the coating, and the shear stresses at the aperture, platelets adhere and aggregate on the collagen surface starting at the area surrounding the aperture. During the course of the measurement, a stable platelet plug forms that

ultimately occludes the aperture. The time required to obtain full occlusion of the aperture is defined as the "closure time" and is indicative of the platelet function in the sample. Accordingly, "closure times" can be compared between subjects receiving a combination therapy and the ones receiving a control therapy in order to evaluate the efficacy of the combination treatment.

EXAMPLE 3

[0443] The laboratory animal study can generally be performed as described in Tanaka *et al.*, *Neurochemical Research*, Vol. 20, No. 6, 1995, pp. 663-667.

[0444] Briefly, the study can be performed with about 30 gerbils, with body weights of 65 to 80 grams. The animals are anesthetized with ketamine (100mg/kg body weight, i.p.), and silk threads are placed around both common carotid arteries without interrupting carotid artery blood flow. On the next day, bilateral common carotid arteries are exposed and then occluded with surgical clips after light ether anesthesia (*see*, e.g., Ogawa *et al.*, *Adv. Exp. Med. Biol.*, 287:343-347, and Ogawa *et al.*, *Brain Res.*, 591:171-175). Carotid artery blood flow is restored by releasing the clips after 5 minutes of occlusion. Body temperature is maintained about 37°C using a heating pad and an incandescent lamp. Control animals are operated on in a similar manner but the carotid arteries are not occluded. The combination therapy is administered immediately and 6 and 12 hours after recirculation in the ischemia group, whereas sham-operated animals receive placebo, which may be, e.g., the vehicle used to administer the combination therapy. Gerbils are sacrificed by decapitation 14 days after recirculation. The brain is removed rapidly and placed on crushed dry-ice to freeze the tissue.

[0445] The brain tissue can then be examined histologically for the effects of combination therapy in comparison to the placebo. For example, each brain is cut into 14 μm thick sections at -15°C. Coronal sections that include the cerebral cortex and hippocampal formation are thawed, mounted onto gelatin-coated slides, dried completely, and fixed with 10% formalin for 2 hours. The sections are stained with hematoxylin-eosin and antibodies to glial fibrillary acidic protein (GFAP), which can be commercially obtained from, e.g., Nichirei, Tokyo,

Japan. Immune complexes are detected by the avidin-biotin interaction and visualized with 3,3'-diaminobenzidine tetrahydrochloride. Sections that are used as controls are stained in a similar manner without adding anti-GFAP antibody. The densities of living pyramidal cells and GFAP-positive astrocytes in the typical CA1 subfield of the hippocampus are calculated by counting the cells and measuring the total length of the CA1 cell layer in each section from 250x photomicrographs. The average densities of pyramidal cells and GFAP-positive astrocytes in the CA1 subfield for each gerbil are obtained from counting cells in one unit area in each of these sections of both left and right hemispheres.

[0446] The effects of the combination therapy in comparison with the placebo can be determined both qualitatively and quantitatively. For example, the appearance of CA1 pyramidal neurons and pyramidal cell density in the CA1 subfield may be used to assess the efficacy of the treatment. In addition, immunohistological analysis can reveal the efficacy of combination by evaluating the presence or absence of hypertrophic GFAP-positive astrocytes in the CA1 region of treated gerbils, since the sham-operated animals should have few GFAP-positive astrocytes.

EXAMPLE 4

[0447] Rat middle cerebral artery occlusion (MCAO) models are well known in the art and useful in assessing a neuroprotective drug efficacy in stroke. By way of example, the methods and materials for MCAO model described in Turski *et al.* (*Proc. Natl. Acad, Sci. USA*, Vol. 95, pp.10960-10965, Sept. 1998) may be modified for testing the combination therapy as described above for cerebral ischemia treatment.

[0448] The permanent middle cerebral artery occlusion can be established by means of microbipolar permanent coagulation in, e.g., Fisher 344 rats (260-290 grams) anesthetized with halothane as described previously in, e.g., Lippert *et al.*, *Eur. J. Pharmacol.*, 253, pp.207-213, 1994. To determine the efficacy of the combination treatment and the therapeutic window for such treatment, the combination therapy can be administered, e.g., intravenously over 6 hours beginning 1, 2, 4, 5, 6, 7, 12, or 24 hours after MCAO. It should be noted that different doses, routes of administrations, and times of administration can

also be readily tested. Furthermore, the experiment should be controlled appropriately, e.g. by administering placebo to a set of MCAO-induced rats. To evaluate the efficacy of the combination therapy, the size of infarct in the brain can be estimated stereologically, e.g., seven days after MCAO, by means of advanced image analysis.

[0449] In addition, the assessment of neuroprotective action against focal cerebral reperfusion ischemia can be performed in Wistar rats (250-300 grams) that are anesthetized with halothane and subjected to temporary occlusion of the common carotid arteries and the right middle cerebral artery (CCA/MCAO) for 90 minutes. CCAs can be occluded by means of silastic threads placed around the vessels, and MCA can be occluded by means of a steel hook attached to a micromanipulator. Blood flow stop can be verified by microscopic examination of the MCA or laser doppler flowmetry. Different doses of combination therapy can then be administered over, e.g., 6 hours starting immediately after the beginning of reperfusion or, e.g., 2 hours after the onset of reperfusion. As mentioned previously, the size of infarct in the brain can be estimated, for example, stereologically seven days after CCA/MCAO by means of image analysis.

EXAMPLE 5

[0450] The following procedures can be performed as described in, e.g., Nogawa *et al.*, *Journal of Neuroscience*, 17(8):2746-2755, April 15, 1997.

[0451] The middle cerebral artery (MCA) is transiently occluded in a number of Sprague Dawley rats, weighing 275-310 grams, using an intravascular occlusion model, as described in, e.g., Longa *et al., Stroke* 20:84-91, 1989, Iadecola *et al., Stroke* 27:1373-1380, 1996,and Zhang *et al., Stroke* 27:317-323. A skilled artisan can readily determine the appropriate number of animals to be used for a particular experiment. Under halothane anesthesia (induction 5%, maintenance 1%), a 4-0 nylon monofilament with a rounded tip is inserted centripetally into the external carotid artery and advanced into the internal carotid artery until it reaches the circle of Willis. Throughout the procedure, body temperature is maintained at 37° ± 0.5°C by a thermostatically controlled lamp. Two hours after induction of ischemia, rats are reanesthetized, and the filament is

withdrawn, as described in, e.g., Zhang *et al., Stroke* 27:317-323. Animals are then returned to their cages and closely monitored until recovery from anesthesia.

[0452] Under halothane anesthesia, the femoral artery is cannulated, and rats are placed on a stereotaxic frame. The arterial catheter is used for monitoring of arterial pressure and other parameters at different times after MCA occlusion. The MCA is occluded for 2 hours, as described above, and treatments are started, e.g., 6 hours after induction of ischemia. In one group of rats (e.g., 6), the combination therapy is administered, e.g., intraperitoneally, twice a day for 3 days. It should be noted that different doses, routes of administration, and times of administration can also be readily tested. A second group of rats is treated with a placebo administered in the same manner. Arterial pressure, rectal temperature, and plasma glucose are measured three times a day during the experiment. Arterial hematocrit and blood gases are measured before injection and 24, 48, and 72 hours after ischemia. Three days after MCA occlusion, brains are removed and frozen in cooled isopentane (-30°C). Coronal forebrain sections (30μM thick) are serially cut in cryostat, collected at 300 μm intervals, and stained with thionin for determination of infarct volume by an image analyzer (e.g., MCID, Imaging Research), as described in Iadecola *et al., J Cereb Blood Flow Metab*, 15:378-384, 1995. Infarct volume in cerebral cortex is corrected for swelling according to the method of Lin *et al., Stroke* 24:117-121, 1993, which is based on comparing the volumes of neocortex ipsilateral and contralateral to the stroke. The correction for swelling is needed to factor out the contribution of ischemic swelling to the total volume of the lesion (see Zhang and Iadecola, *J Cereb Blood Flow Metab*, 14:574-580, 1994). Reduction of infarct size in combination therapy-treated animals compared to animals receiving placebo is indicative of the efficacy of the combination therapy.

[0453] It should be noted that all of the above-mentioned procedures can be modified for a particular study, depending on factors such as a drug combination used, length of the study, subjects that are selected, etc. Such modifications can be designed by a skilled artisan without undue experimentation.